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OBSERVATIONS ON THE VITALITY OF THE NEWBORN

BY

F. E. HYTTEN*

From the Department of Midwifery, University of Aberdeen

(Received for Publication February 14, 1951)

Vitality, defined in the dictionary as ' the capacity to thrive and endure,' is a summation of all assimilative, metabolic, circulatory, and protective functions. It can be measured crudely, in large groups, by mortality and morbidity rates, but since such rates are determined by the reaction between groups of individuals and a variable environment, they may be difficult to interpret. Some observers (Stuart, 1945) used measures such as size at birth or degree of osseous development in an attempt to demonstrate differences of quality in infants, but size and stage of development are not necessarily correlated with efficiency of function. Baird (1949) has posed the question, ' How does one tell whether a particular baby is more vital than another ? ' Some measure is necessary if we are to correlate vitality with the mother's health and diet during pregnancy. Some idea may be obtained by noting the presence or absence of foetal distress during labour and the child's behaviour after birth. The vigour of its movements is difficult to measure, and its ability to suck depends on the type of breast and nipples, the milk supply, and the efficiency of the mother and nurse.

General clinical assessment of vitality is highly subjective and hence has limited scientific value. It was considered that objective assessment of the more accessible neonatal reflexes might be useful. The interpretation of tests carried out during the first week of life should not be unduly complicated by the influence of the general extra-uterine environment. This paper deals with the sucking reflex, the grasp reflex, muscular power, and power of coordinating upper limb action. The first of these is bound up with ability to obtain nourishment and the others are probably associated with the ability of a baby to protect itself. Performance on test, therefore, should have some relationship to the ' capacity to thrive and endure.'

Initial studies were made of 100 unselected normal infants, followed by studies of 80 normal offspring of primiparae. A ' normal ' infant was defined as one weighing more than 5½ lb. at birth, without any obvious physical abnormality, and requiring no more than routine care in the lying-in wards of a maternity hospital.

Methods

Sucking Reflex. Fig. 1 shows the apparatus used here. An Allenbury-type teat was connected by 2 mm. bore pressure tubing, both to a recording manometer and to a milk supply. The hole in the teat was large (4-5 mm. diameter) and was cut irregularly so that it could not be sealed off by the infant's tongue. Corrugated rubber was placed in the teat cavity to prevent collapse. The manometer itself had a constriction in the base of the U-tube to counter the effect of inertia of the mercury. The actual response of the mercury to sudden load and release is shown in the standardization curve (Fig. 2). With this response, the manometer was found to be sensitive enough to the relatively slow rhythm of sucking. Waste space in the apparatus was reduced to less than 10 ml. by keeping connecting tubes narrow and short. Warmed milk was supplied from a reservoir and the flow regulated 5-10 ml. a minute by means of a drip-feed system controlled by a screw clamp.

Up to the fourth day of life the majority of infants would suck a dry teat for some minutes without tiring, and could not cope with more than about 1 oz. of milk a minute without choking. After the fourth day most infants refused to suck for more than 10 to 20 seconds without reward, and were able to handle milk flows up to about 1 oz. a minute without choking.

It was found that the sucking response of infants remained constant when the temperature of the milk was maintained between 20° and 40° C. (confirming Jensen, 1932) and over a wide range of rates of milk flow. Careful tests were carried out on six infants to see if the response on the apparatus resembled that on the breast. During breast-feeding a tube connected to the manometer was inserted into the corner of the infant's mouth. Performances at the breast were found to be indistinguishable from those on the apparatus.

Records were taken on the second, fourth, sixth and eighth days of life, during the fourth hour after a feed,

* Walter and Eliza Hall travelling research fellow.

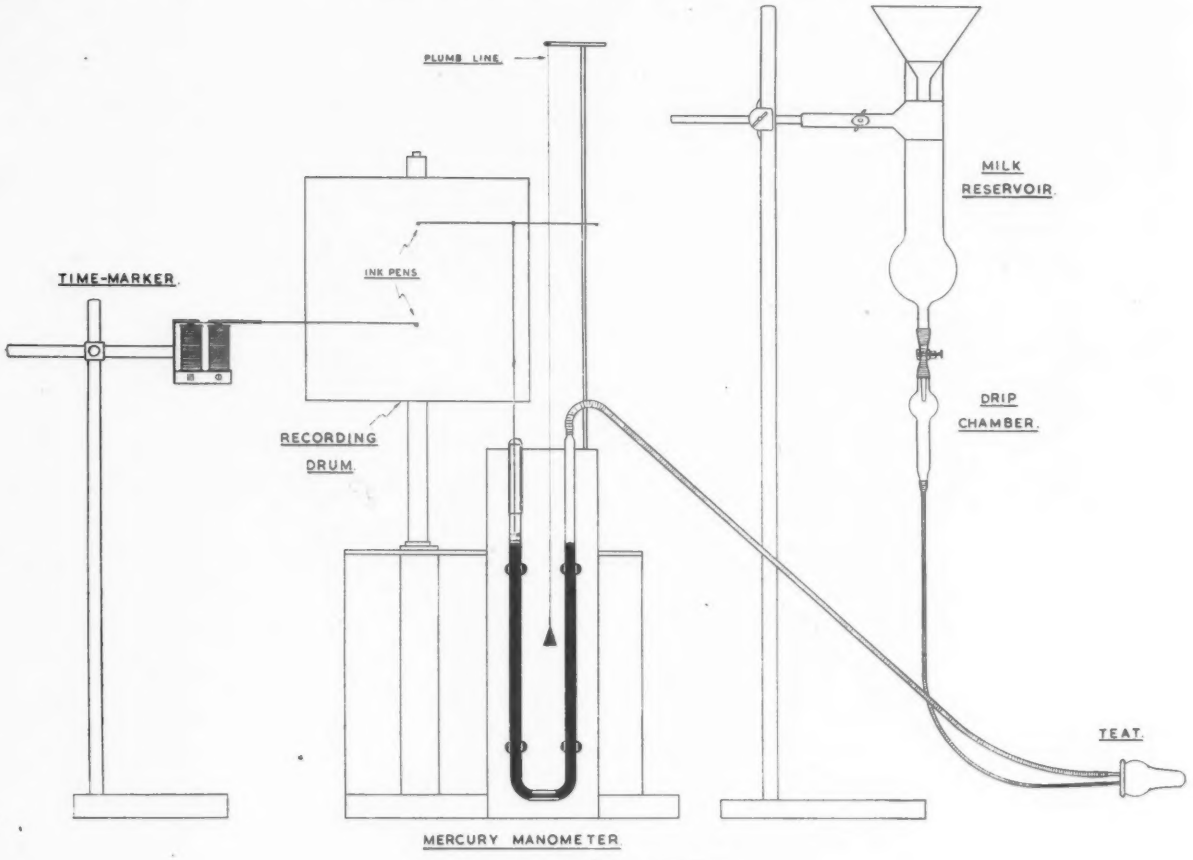

FIG. 1.—Sucking apparatus.

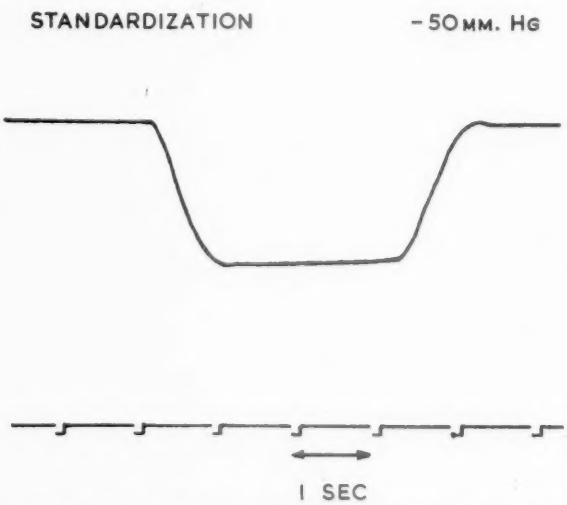

FIG. 2.—Standardization of manometer by sudden decrease of pressure to —50 mm. Hg followed by sudden release to atmospheric pressure.

usually just before the 2 p.m. or 6 p.m. feeds. The first four minutes of sucking were recorded, as it is recognized that the bulk of a breast feed is obtained in this time (Smith and Merritt, 1922).

Tracings could be differentiated in terms of average sucking pressure, maximum sucking pressure, time during which active sucking was in progress, and time during which a negative pressure was maintained with or without sucking movements. In a typical record, the infant begins to suck at once, with a flourish, and after 15 to 30 seconds settles down to a steady sucking rhythm, half or three-quarters as great as its original maximum. Active sucking and swallowing might be maintained for anything from 10 to 100% of the total duration of the record. It should be noted (Fig. 3) that sucking and swallowing excursions take place not from the line of atmospheric pressure but from a line of mean negative pressure determined by the individual infant. Sucking and swallowing can usually be differentiated. Sucking is associated with a relatively small swing of the mercury, usually about 10 mm.; in swallowing, the swing becomes two or three times larger. A swallow appeared to take place after about four or five sucks when the milk flow was small, but as the milk flow was increased there might be a swallow after each suck, or even continuous

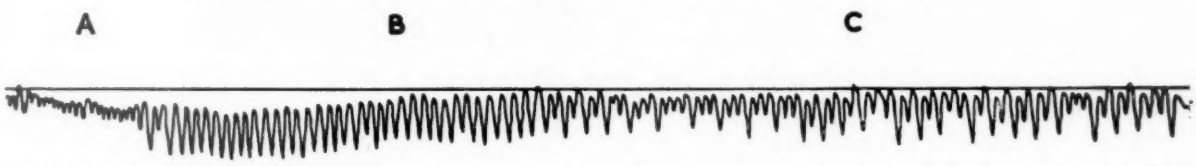

FIG. 3.—Tracing of intra-oral pressure showing A, sucking; B, swallowing; and C, mixed sucking and swallowing.

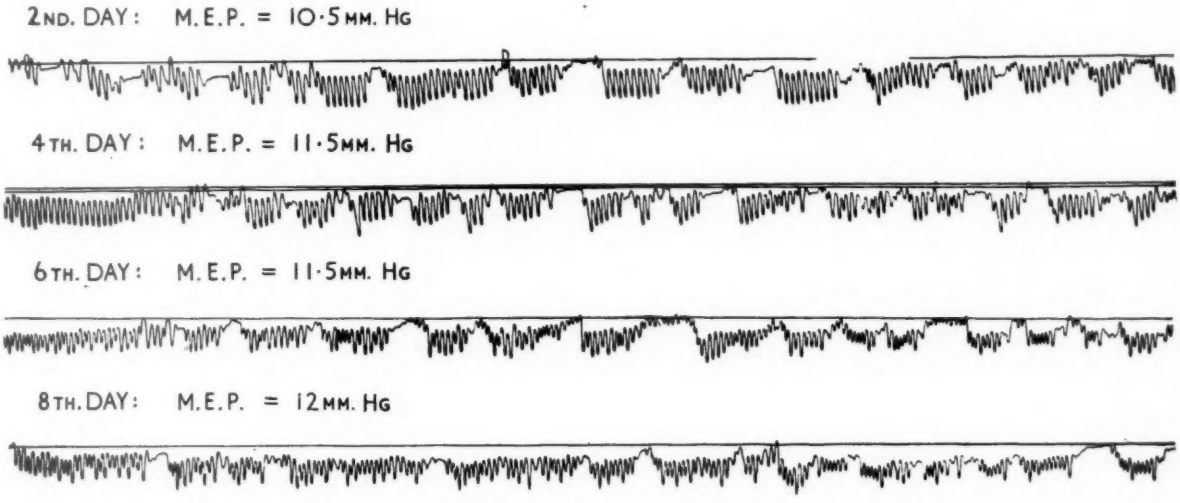

FIG. 4.—Four successive tracings of one infant demonstrating constancy of performance. (M.E.P. = mean effective pressure.)

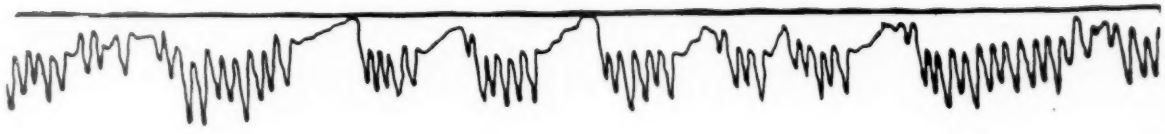

FIG. 5.—Section of tracing demonstrating the slow fall in 'suction' pressure in the mouth as it fills with milk during a pause.

swallowing. Uninterrupted sucking and swallowing was not usual, and, as a rule, the tracing was broken up into periods of activity lasting 10 to 20 seconds, separated by intervals of one or two up to 20 seconds, during which pressure slowly regained atmospheric pressure as the mouth filled with milk, or suddenly if the mouth opened. Four out of every five babies sucked and swallowed actively for between 60 and 90% of the recording time, and in nine-tenths of the cases some degree of negative pressure was maintained for 70% or more of the time.

Figs. 3, 4, and 5 show some typical tracings. It was found that most infants gave a characteristic tracing on all four test days. The pattern of sucking was more constant than the actual mean pressure. In 66% of cases the mean effective pressure (M.E.P.) did not vary by more than 2 mm. Hg in trials over the four test days; 24% of cases improved by more than 2 mm. Hg, 4% deteriorated, and 6% gave haphazard results. The liability to improve or remain steady was not associated with the normal supply of breast milk or with bottle feeding (Table 1).

Several ways of evaluating the tracings were studied, and the best was found to be the mean effective pressure (M.E.P.) of the whole record. The value of M.E.P. is obtained from the formula

$$\frac{\text{(Area enclosed by tracing and by line representing atmospheric pressure)} \times 2}{\text{(Length of tracing)}}$$

The area is measured with a planimeter. The factor 2 is used because one limb of a manometer records pressures at half their true value. M.E.P. thus takes into account both the average degree of suction and the proportion of recording time during which suction is maintained. The value is not materially affected by the amount of swallowing. As used hereafter, it refers to the mean of four measurements made on the second, fourth, sixth, and eighth days of life. It should be noted that the pressure is negative. To avoid confusion and complication, the negative sign will be omitted and greater or lesser M.E.P. will refer to greater or lesser degrees of negative pressure or suction.

The values of M.E.P. for the 180 normal infants were normally distributed around a modal point at 10 mm. Hg (Fig. 6). Extremes of 2 mm. and 26 mm. were recorded,

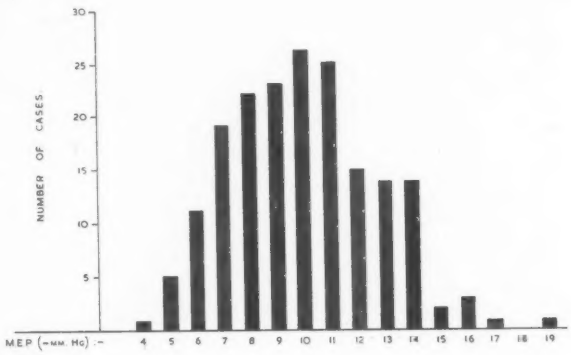

FIG. 6.—Frequency distribution of mean effective pressure in 180 cases.

both in abnormal cases. The greatest M.E.P. recorded in a normal infant was 22 mm.

Other authors have evaluated the sucking effort in terms of the greatest negative pressures recorded. Cramer (1900) and Gunther (1945) obtained negative pressures up to 70-200 and 45-100 mm. Hg respectively. In the present study no suction greater than 50 mm. Hg has been recorded. It is probable that higher values reported by other workers were obtained by the use of faulty apparatus. I was able to obtain similarly high values by using an undamped manometer and a pin-hole teat (Fig. 7). It seems that if the mercury can oscillate relatively violently and if the infant's tongue can seal off the teat or tube, a valve-like action causes negative pressure to build up in the apparatus until it greatly exceeds the true intra-oral pressure.

Grasp Reflex. The attempt was made to induce infants to grasp a thin, rubber-covered rod attached to a spring balance, with the idea of measuring the pull required to break the grip. The method had to be

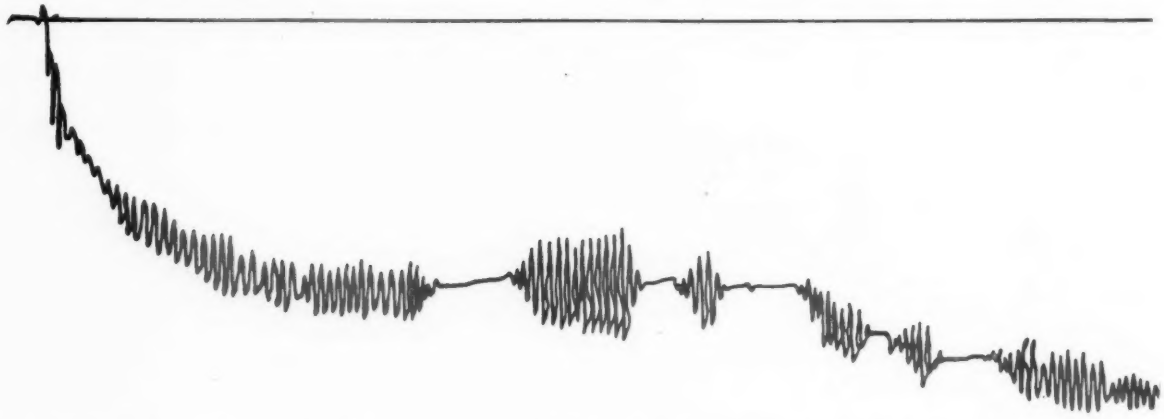

FIG. 7.—The effect of an undamped manometer used in conjunction with a 'pin-hole' teat. Maximum pressure shown is —130 mm. Hg.

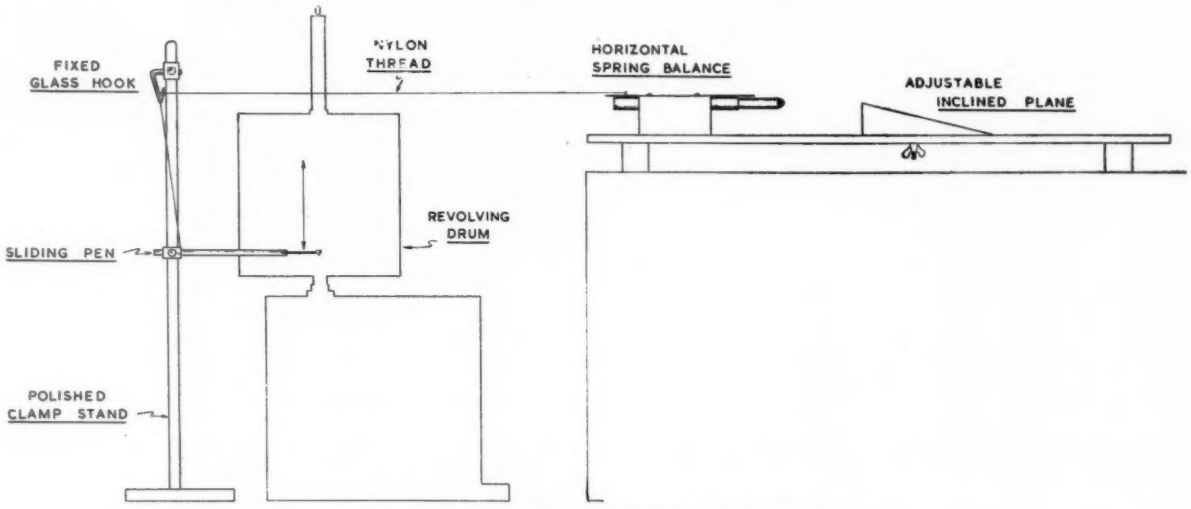

FIG. 8.—Apparatus for recording pull factor.

abandoned, because many infants were uncooperative and because results, when obtained, appeared to be completely haphazard. No results are therefore presented.

Muscular Power. The infant was placed on a table with its lower limbs extended by hand pressure to slightly less than full extension at the knee. Anklets were tied on, and tapes from them fixed to a horizontal spring balance giving about $\frac{1}{2}$ in. movement per lb. A cold object placed on the infant's chest invariably caused a forcible flexion of the lower limbs. For the first 100 cases the strength of the pull was measured by placing a 'rider' beside the marker on the spring balance, which remained at the highest figure obtained. For the final 80 cases (for reasons given below) it was found desirable to take into account both the average strength of the pull and the time during which it was maintained, and this was done by attaching the marker of the spring balance by a cord over a pulley to a recording drum (Fig. 8). With this new apparatus continuous cold stimulation was applied to the infant's chest and recording was discontinued when the record fell back to 1 lb. weight or less.

The following values obtained from these records were used: (*a*) the 'muscular power index,' which is simply the greatest pull exerted, expressed as a percentage of body weight; and (*b*) the 'pull factor,' which is the product of the time in seconds during which active contraction was present and the average tension exerted during this time, expressed as a percentage of body weight. Fig. 9 shows a typical tracing.

Coordination. In all 180 cases the tip of the infant's nose was held lightly and its reactions observed. On a first trial most infants thrashed wildly with all four limbs, shook their heads, and occasionally responded by mass extension. A very few made an apparently deliberate attempt to remove the hand. On succeeding trials some infants quickly learnt to remove the nuisance by using their upper limbs, while others took longer. The observer's fingers were removed from the infant's nose immediately the infant struck the hand. Response was graded as follows:

'Very good' if there was an apparently deliberate attempt to brush away the observer's hand within 5 seconds	5·6%
'Good' if the attempt was made between 5 and 15 seconds	34·0%
'Fair' if between 15 and 30 seconds ..	43·4%
'Poor' in other cases	17·0%

Each infant was required to repeat the performance at least once, and usually twice, at each trial.

Other Data. The following specific information was available for all or some of the infants tested:

CLINICAL GRADING. The first 100 infants were graded independently by three independent assessors who were given the following information: the physical state of the infant immediately following birth; the muscle tone and general physical appearance; the activity reaction to stimulation; any clinical observations during the first

FIG. 9.—Two typical recordings of pull factor. The first infant gives an average pull of 2·2 lb. for nine seconds and the second infant an average pull of 2·6 lb. for 14 seconds before falling to the '1-lb.' line.

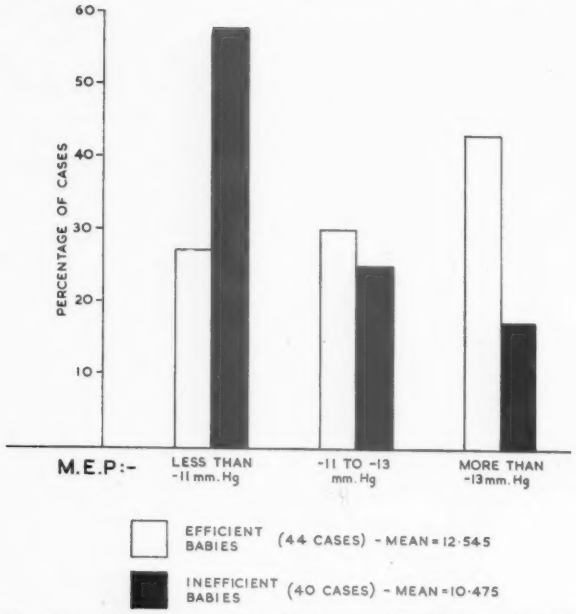

FIG. 10.—Distribution of ' efficient and inefficient ' babies arranged according to sucking performance.

week of life, e.g. difficulties with 'mucus,' jaundice, and cyanosis; the feeding performance as judged by test weighing; and the weight curve.

Naturally, there were variations in the grading of individual infants by each assessor, but in no case did the three assessors place any infant in three different grades. In 42% of cases all three assessors agreed completely. In the remainder, the majority verdict was used. The distribution obtained was:

' Very good '	14%
' Good '	60%
' Fair '	22%
' Poor '	4%

The relatatively close agreement obtained was doubtless partly due to the fact that the three clinicians concerned have worked in the same unit for some time and have many standards in common.

MILK-GETTING CAPACITY. The first 100 infants were divided arbitrarily into two groups. ' Efficient ' infants were those who obtained 2·2 oz. (63 ml.) breast milk per lb. body weight in 24 hours before the tenth day, or alternatively emptied both breasts so thoroughly that no more than 4-5 ml. could be expressed after feeding. ' Inefficient ' were those who obtained less than 2·2 oz.

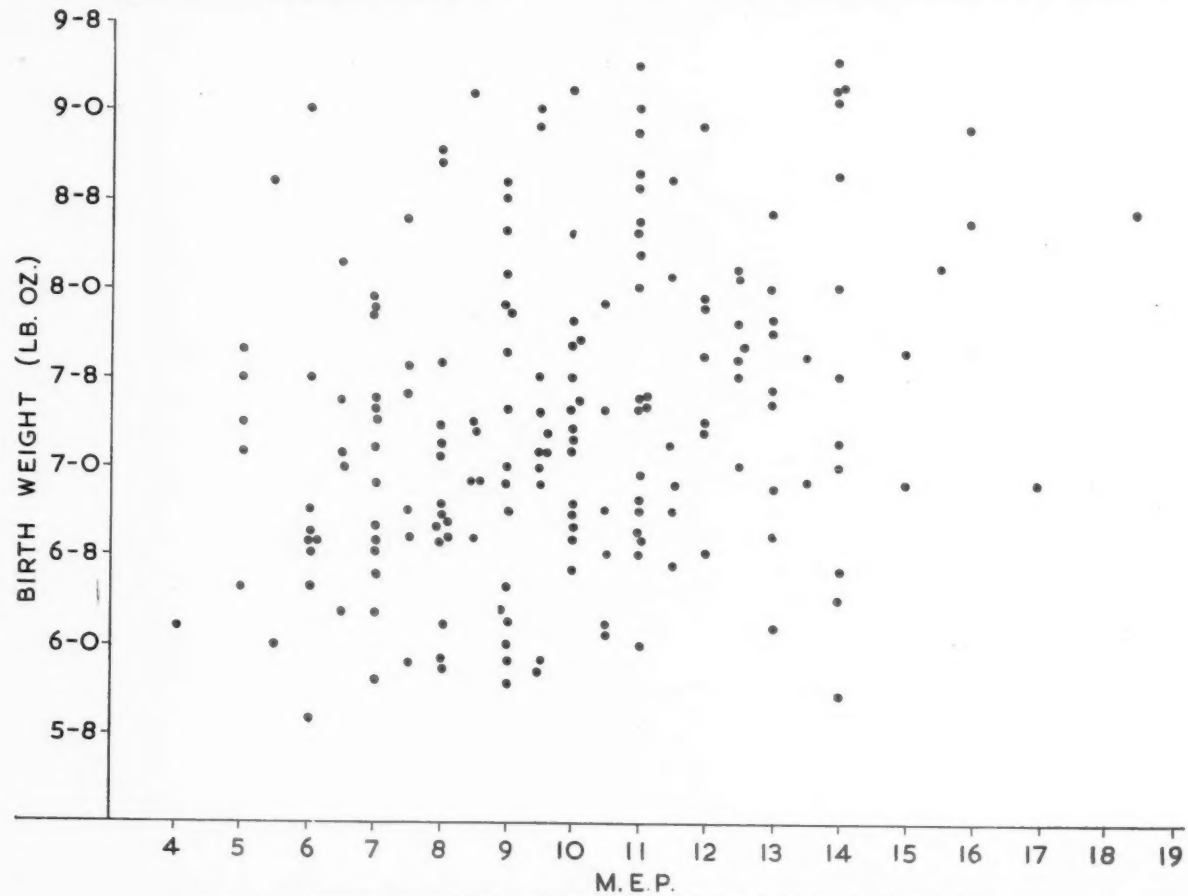

FIG. 11.—Correlation of birth weight and M.E.P. ($r = 0{\cdot}30$ $P > 0{\cdot}001 < 0{\cdot}01$).

(63 ml.) per lb. body weight in 24 hours and left milk in the breast.

(The value of 2·2 oz. (63 ml.) was chosen because it divided the cases into two groups of roughly equal size.)

BIRTH WEIGHT. The birth weight of all infants was noted.

COMPOSITION OF BREAST MILK. Milk of the seventh day post-partum was expressed manually for 24 hours, and samples of the pooled yield were analysed for fat, protein, and lactose in 60 of the final cases.

Results

M.E.P. was evaluated with milk-getting capacity. Fig. 10 shows that babies who emptied the breasts or who got more than 2·2 oz. milk per lb. body weight by the tenth day were, on the whole, more powerful suckers, as assessed by M.E.P. The correlation is highly significant ($P. < \cdot 001$).

It might be argued that heavier babies had greater ability to suck as well as a better milk supply, so that this correlation might be to some extent fortuitous. Birth weight and M.E.P. are correlated to a slight degree (Fig. 11) but not birth weight and milk-getting capacity. The correlation between M.E.P. and milk-getting capacity would appear, therefore, to be independent of birth weight.

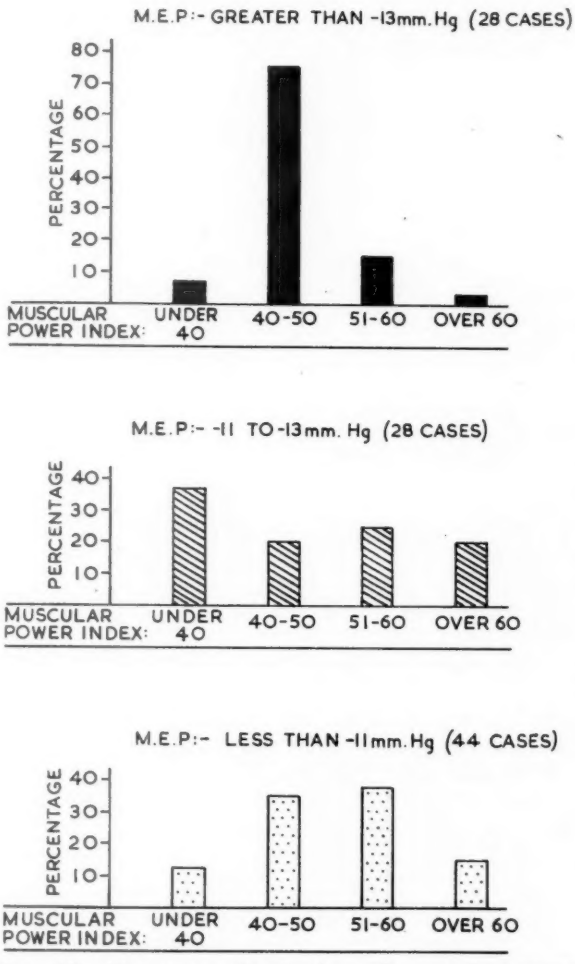

FIG. 12.—Frequency distribution of muscular power index in infants, arranged in three groups for M.E.P.

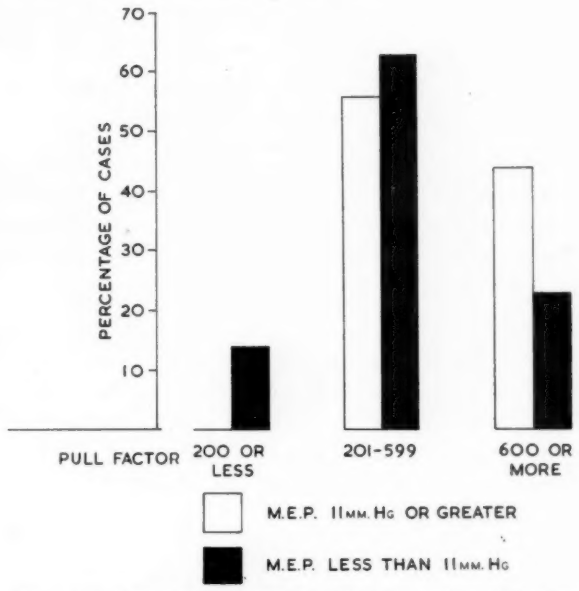

FIG. 13.—Correlation between M.E.P. and pull factor.

M.E.P. was *inversely* correlated (significant at 1% level) with the fat content of the seventh day milk. The meaning of this curious finding is not clear. There was no correlation between M.E.P. and seventh day milk volume, nor with milk constituents other than fat.

In the first 100 cases it was found that M.E.P. and muscular power index were negatively correlated to a significant degree. Fig. 12 shows that among babies with a high M.E.P. the muscular power indices tended to be concentrated between 40 and 50 whereas with lower M.E.P. levels the scatter was very much wider. A possible interpretation of this distribution is that the former group of babies gave more sustained and purposeful flexion of the lower limbs under test, whereas the latter tended to give ill-sustained but momentarily more powerful jerks. It was for this reason that time as well as strength of pull was measured and expressed as ' pull factor.' In the second series of 80 babies it was found that, whereas muscular power index and M.E.P. were again negatively correlated, M.E.P. and ' pull factor ' were positively correlated (Fig. 13). Fig. 14, however, shows this correlation to be low. The pull factor is probably, therefore, a better measure of muscular action.

The values of pull factor obtained did not seem to be related to muscle tone as assessed clinically. Their importance, if any, can only be determined by a follow-up study to find out, for example, whether babies with better performance showed evidence of better locomotion later in growth.

Coordination, as tested, was found to be correlated significantly with the combined clinical assessment, but not with any other measure available in this series. The meaning of the test is not entirely clear, but apart from being a crude test of coordination of muscle action, it may have some relation to a baby's ability to learn.

The various tests did not necessarily agree with one another in a given case. The reason may be that different kinds of function may not be equally developed. Not enough work has been carried out to show definitely which test is the most useful in assessing vitality. The human infant is, however, not expected to do much more than feed itself, and survives without the need for self-protection. For this reason, the M.E.P. should, theoretically at least, be the most useful index of vitality. The M.E.P. and coordination were positively correlated with the clinical grading of the first 100 infants, the correlations being significant at the 1% level. Muscular power index was negatively correlated, but its significance is doubtful. The correlations were, however, not high for individual babies. The clinical grade could be predicted in only about 75% of cases when a regression equation containing values of M.E.P. and coordination were used. This lack of correlation in many individual cases between the clinical assessment and the M.E.P. seems most likely to have been due to difficulties in grading babies clinically.

Discussion

The Sucking Reflex. Clinical evaluation of feeding is highly unreliable. Norval (1946) in a study of 50 infants, found that only 20% were vigorous feeders, and that 76% tended to fall asleep and required stimulation. Experience in this series indicates that the vigorous, busy-looking infant does not have the consistent performance of the relaxed infant, who may well be sucking thoroughly though sometimes apparently asleep. The weight curve is commonly used as a criterion of successful feeding, but cannot be reliable, since it represents a balance between the unknown caloric intake of the infant and its equally unknown metabolic level.

The sucking reflex is one of the earliest reflexes to appear, having been demonstrated as early as the third month *in utero* (Windle, 1940) so that there can be no question of absence through immaturity.

Most observers, however, maintain that ' sucking '

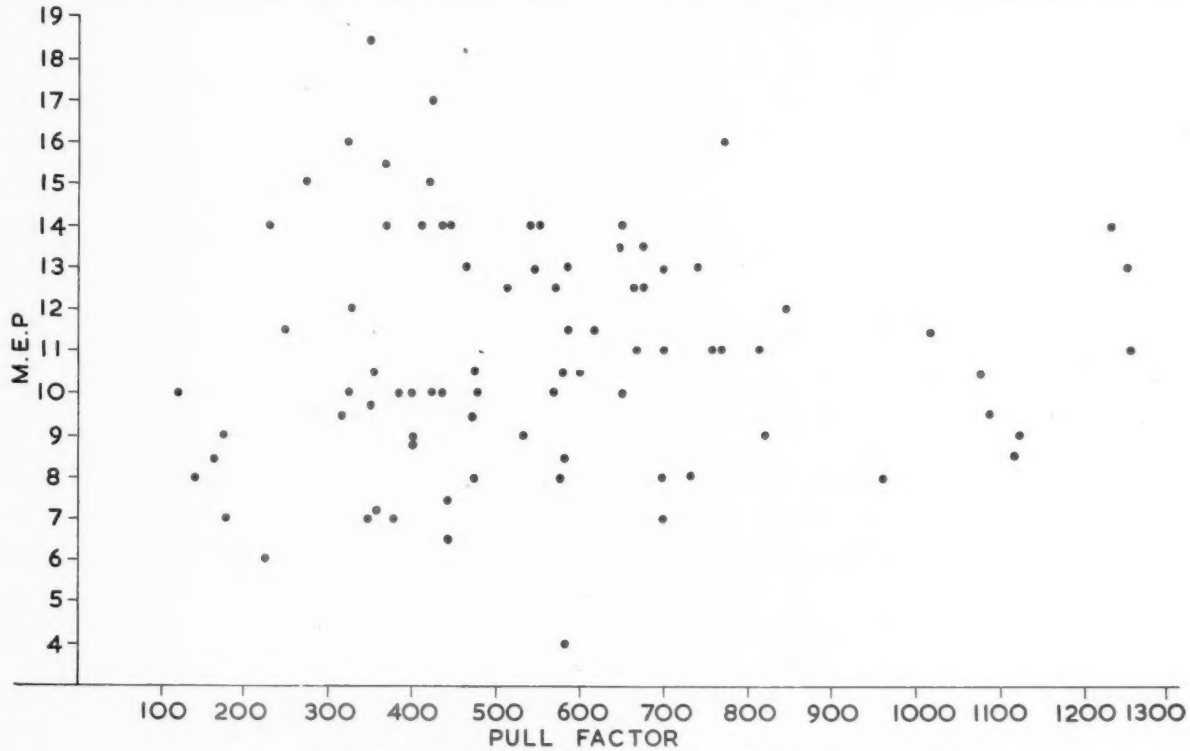

FIG. 14.—Correlation of M.E.P. and pull factor.

as applied to feeding is a misnomer, and the actual force which extracts the milk is a type of oral expression carried out by the jaws. This idea has been firmly stressed in the literature for at least 50 years and in textbooks from Pfaundler and Schlossman in 1908 to Naish in 1948, but no real evidence is submitted.

Statements denying that sucking is the force which obtains milk from the breast have been punctuated, however, by work attempting to demonstrate the sucking potential of infants. On only one occasion has this been correlated with milk-getting capacity. Cramer (1900), by a method which he does not describe, gives actual pressures at which he maintains the breast begins to secrete milk, varying from 10 mm. Hg to – 50 mm. Hg for different breasts.

In the other studies, the sucking appears to have been considered in relation to other factors than feeding ability. Gunther (1945) was demonstrating a cause of cracked nipples, Jensen (1932) discrimination of taste and temperature sensation, and Kasahara (1916) was only interested in the variation of sucking pattern in normal and abnormal infants.

Theoretically, the sucking power of an infant is a valid index of the ability to remove liquid from a reservoir at atmospheric pressure, but it must be admitted that it does not necessarily reflect its ability to remove milk from the rather more complex human breast. However, some accessible and objective criteria of feeding ability are required, and sucking does seem to represent a reasonable starting point. It is, of course, possible that the infant might be influenced in its performance by its experience at the breast. For example, a baby with an initially low M.E.P. might, if nursed by a mother with free-flowing milk, learn to diminish its sucking performance without prejudice to its milk intake. Alternatively, the infant confronted by a scanty supply might exert itself and increase its performance in an attempt to better its intake.

Although Aldrich (1945) maintains that an infant exists on a purely subcortical level and cannot ' learn ' habits, Marquis (1941) has shown that feeding schedules can be ' learned ' in 10 days, and Fredeen (1948), who spoon-fed a series of infants from birth, states that the sucking reflex can be made to disappear entirely after one week. The possibility that an infant is able to learn from experience within the first week of life stimulated the investigation shown by Table 1. There is no significant variation in M.E.P. which would indicate adaptation of sucking performance to the ease or difficulty of obtaining milk at least within the first eight days.

Measurement of Muscular Power. This application of the Moro reflex has not been previously described and it is reasonable to suppose that the method used will demonstrate the maximum power available from flexion of the lower limbs.

Knop (1946) carried out an experiment in which she lifted infants by their hands and attempted to grade the vigour of their reaction by the degree of spontaneous flexion at the elbow, but reached no significant results.

The use of the muscular power index admittedly gives an advantage to the leaner baby whose mass is composed of a higher proportion of muscle, but in the absence of the elaborate radiological techniques for the estimation of muscle mass, it is the only practicable method of bringing results to a comparable level.

The distribution of muscular power index in the first series of babies is striking. If the index occurring most frequently in the best suckers, that between 40 and 50, is to be accepted as the ' ideal ' or ' normal,' then it must also be accepted that an infant's muscular performance can not only be too weak but also too powerful. This is difficult to believe. A more reasonable interpretation would be that the answer lies not in the maximum contraction but in the way it is achieved. The moderate contraction might represent a more sustained and purposeful movement than the more powerful but momentary one. The results, using the power factor, lend weight to this hypothesis, that although the poorer sucking group have a more potent initial contraction, their power of sustained muscular contraction is less.

Coordination. I can find no reference to the use of this test in the literature.

Stirnimann (1937) discusses the reactions of infants having their hands in gloves and regards the movements associated with attempts to remove this irritation as instinctive.

The test itself not only demonstrates the ability of the infant to coordinate its upper limbs, but perhaps more importantly, shows its ability to learn from experience, a simple form of self protection.

Irwin (1942) has pointed out that there is no means at our disposal of assessing the mental prowess of an infant, but the ability to learn which has been mentioned in reference to sucking, may have this second significance. Whereas it may confuse the assessment of true potential sucking power, the ability to learn from the environment is a function which itself requires evaluation. In conclusion, it should be emphasized that this work merely points in the approximate direction of the answer to the problem. To find a satisfactory measure of vitality with which to correlate such things as maternal health and diet is inevitably a long and intricate task.

Summary

In an attempt to find some objective index of vitality, which has been defined as 'the ability to thrive and endure,' four functions of the newborn normal infant have been studied.

The mean effective pressure of sucking is correlated with the milk-getting capacity of the infant, with a clinical grading of general vitality, and, to a lesser extent, with birth weight.

There is no apparent variation in sucking performance during the eight days following birth which can be attributed to difficulty in breast-feeding.

The muscular power index, which implies the maximum power developed by a single muscular contraction, is negatively correlated with sucking performance, but the pull factor, indicative of sustained muscular action, is positively correlated, demonstrating that the better suckers have a more sustained and apparently purposeful muscular action than the poorer ones. The degree of correlation is, however, low.

Coordination, which shows not only the power of actual coordination, but also the ability to learn, is correlated with the clinical index of general vitality, but not with the other objective measurements.

The grasp reflex was discarded as being far from fully understood, no certain method of elicitation being known and results being quite haphazard.

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TABLE 1

CHANGES OF SUCKING PERFORMANCE IN RELATION TO TYPE OF FEEDING

Type of Milk Supply	Steady* Performance (66 cases)	Improvement of Performance (24 cases)
Sufficient or more than sufficient	73%	66%
Insufficient (complementary feeds given) ..	25%	25%
Artificially fed from birth	2%	9%
	100%	100%

*In 14% of 'steady' performers, and 13% of 'improved' performers, there was some technical difficulty in feeding, due to inverted nipples, etc.

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PHENYLKETONURIA WITH A STUDY OF THE EFFECT UPON IT OF GLUTAMIC ACID

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Since Fölling (1934) in Norway first drew attention to the association of mental defect with the excretion of phenylpyruvic acid in the urine, this syndrome has been reported from many parts of the world. In institutions for mental defect it has become possible to separate, by a simple urine test, a group of patients of the lower grades who are found also to have certain general physical characteristics in common. Names for this inborn error of metabolism range from the descriptive but unwieldy term 'phenylpyruvic oligophrenia' to 'Fölling's disease.' 'Phenylketonuria' was suggested by Quastel and adopted by Penrose (1935).

It has been studied in great detail as a problem in genetics, chiefly by Penrose (1946) and Munro (1947) in Britain, and by Jervis (1939) in the U.S.A. The conclusion reached is that it is inherited as a Mendelian recessive characteristic. In a large series of families, it is found that the proportion of affected siblings is about one in four, and that there is a greater than average incidence of consanguinity amongst the parents (in Munro's series, 10% compared with a normal rate of 1%). Fortunately the fertility of phenylketonuric patients is so low that it rarely occurs in both parents and offspring. In a series of 50 cases (Jervis, 1937) only one parent was definitely affected.

It has been suggested (Penrose, 1935) that depression with persecutory ideas and other types of mental disturbance are more common amongst the parents of these patients than amongst the average population. Munro (1947) compared the parents from 47 phenylketonuric families with the parents of a large group of idiots and imbeciles of other types, and found the incidence of psychoses to be about the same.

Incidence

The incidence can be estimated only from the proportion of cases discovered amongst mental defectives in institutions. Munro (1947) finds that it occurs in 1·2% of idiots and imbeciles and, knowing the approximate number of these in the general population, calculates a total incidence of between 2 and 6 per 100,000 in Britain. This excludes the very few who are above the imbecile grade. Jervis (1937) finds phenylketonuria in 0·522% of mentally defective patients of all grades in institutions in the U.S.A., as compared with 0·04% in Switzerland (Brugger, 1942) and 1·34% in Norway (Fölling, 1934).

Such estimates are inevitably approximate, and are not strictly comparable because of the variations in the proportion and grade of mentally defective patients who are admitted to institutions in different communities. Some of the difference may, however, be racial, as no cases have been reported amongst Jews or Negroes.

Age

Phenylketonuria has not been demonstrated at birth, but Munro (1950) in a personal communication states that he has seen it at the age of 6 weeks. Apart from this, Cases 1 and 5 here described are among the youngest on record at the time of writing.

In a suspected case, aged 2 months, reported by Delay, Pichot, Delbarre, and Taseel (1948), the youngest member of an affected family, it is said of the urine that '*La réaction de Fölling n'y est pas franchement positive.*'

Clinical Picture

Though it is essential to find phenylpyruvic acid in the urine before making the diagnosis, there are certain rather inconstant clinical features which, occurring together in one patient, may suggest it to the observer so strongly that the urine examination is merely a confirmatory test.

Those who see these patients frequently can

recognize a facial similarity in many of them which is difficult to define. One of the most constant physical features is the relative lack of pigment in the hair and eyes. In one series (Jervis, 1937) 86% were blondes and 66% had blue eyes. A blonde patient, 38 of whose relatives were dark, is described by Delay and Pichot (1947), and another patient of Sicilian parentage is cited, members of whose family had been dark for three generations. This suggests that the fairness of the hair is related to the biochemical disorder. Cranial measurements tend to be small in some cases, but with no characteristic skull shape. The large size of the maxilla, which is particularly noticeable in Case 3 (Fig. 3b), may or may not be accompanied by wide spacing of both upper and lower incisor teeth (Fig. 2b). Roughness of the skin, with either a dry papular eruption on the extensor aspects or diffuse eczematous patches, is also common. There may be kyphosis and dwarfing in later childhood. Reports of abnormal signs in the central nervous system differ. In one large series of patients fully examined 70% were said to have increased muscle tone and exaggerated deep reflexes, the plantar responses being flexor (Jervis, 1937). Others disagree, and state that ordinarily there is no increase in muscle tone (Penrose, 1949). Certainly it was not a feature of any one of our five cases. Repetitive movements, particularly of the fingers, are common, but they are organized and are not suggestive of release of cortical control as in choreo-athetosis. The gait, when walking is possible, is clumsy and the body is held rather rigidly, bent forwards. Petit mal, or less commonly, major epilepsy, are frequent complaints.

Examinations of the cerebrospinal fluid have shown no abnormality, apart from a high content of phenylalanine (Jervis, Block, Bolling, and Kanze, 1940). Air encephalograms in 11 cases (Jervis, 1937) showed in some a moderate dilatation of the ventricles, and in others an increased amount of air in the subarachnoid space. Electroencephalograms are not characteristic, but, as in our cases, frequently show evidence of epilepsy.

On the whole these patients are not as unattractive physically as one would expect from the severity of the mental defect. Most are idiots with intelligence quotients below 20, the remainder being mostly imbeciles, with a very occasional case of higher grade.

Galactose-tolerance tests have been carried out in nine cases (Cowie, 1950, personal communication) and in three of these the results indicated a considerable degree of liver dysfunction.

The Urine Test

Testing for the presence of phenylpyruvic acid is so simple that it can easily be done as a routine in all patients with mental defect attending an out-patient clinic. To 5 ml. of urine 0·5 ml. of 5% ferric chloride is added. A deep green, which reaches a maximum intensity within three minutes and fades gradually, is a positive result.

FIG. 1.—Case 1 at 23 months.

Prognosis

The biochemical disturbance does not seem to have any deleterious effect upon bodily health, and the mental state does not progressively deteriorate after the age of 1 year. There is, however, no record of a patient having shown any striking increase in intelligence.

The chance of a subsequent child being also affected is one in four.

Pathology

Reports of necropsies are remarkably scarce and at the time of writing only two are known to have been published.

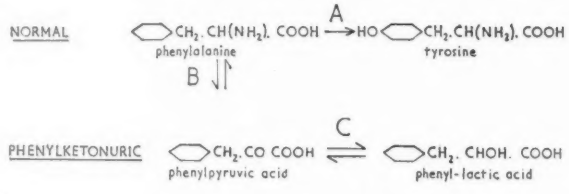
The first (Penrose, 1939) was of a boy of 9 years who died of intercurrent pulmonary infection. The findings of importance were a brain of normal size and weight with no definite histological abnormality, and the presence of many small, tense swellings resembling neurofibromata along nerve trunks,

particularly the vagi, phrenics, the pudendal and coeliac plexuses, and the left sciatic nerve. The liver was reported as normal.

The second (Coquet, Myle, Nyssen, and van Bogaert, 1944), aged 12 years, died in 'cachexia,' the body being greatly dehydrated. Although microscopic examination of the brain was carefully carried out, the findings were mostly such as might be explained by the general cachectic state at death. There was, however, some glial proliferation in the region of the centrum ovale, and some lymphocytic cuffing around vessels in the leptomeninges and cortex. The liver showed 'perilobular' fatty degeneration and congestion in the intertrabecular capillaries.

Biochemical Basis

The error in metabolism lies in the inability of these patients to convert phenylalanine to tyrosine, the normal pathway for phenylalanine metabolism (reaction A). The phenylalanine, which has a high kidney threshold, accumulates in the blood and cerebrospinal fluid, and 'spills over' into the urine (Jervis, 1947). Some of the phenylalanine is converted, either by transamination or by oxidative deamination, to phenylpyruvic acid (reaction B); some of this is reduced to phenyl-lactic acid (reaction C), and probably undergoes other changes. Both of these acids have low kidney thresholds and appear in the urine in large amounts, but cannot be detected in the blood or cerebrospinal fluid by the methods at present available.



Reaction A takes place in the normal liver, while nothing is known of the sites of reactions B and C. An alternative view is that phenylpyruvic acid is a normal intermediate product of phenylalanine metabolism, and is normally converted to p. -hydroxyphenylpyruvic acid, and this in turn to tyrosine. On this supposition the metabolic block in these patients lies in the inability to hydroxylate phenylpyruvic acid (Penrose and Quastel, 1937).

Case Reports

Case 1. Michael H. (Fig. 1), aged 18 months, was born by normal delivery after a normal pregnancy and weighed 7 lb. 5 oz. Nothing abnormal was noticed in the newborn period.

The father and mother were of normal intelligence and unrelated, having been born in widely different parts of the country. A brother, aged 6 years (Case 2), was an idiot with phenylketonuria; there were no other siblings and there had

FIG. 2a.

FIG. 2a.—Case 2, at 6 years, showing bizarre posture.

FIG. 2b.—Case 2, to show the wide space between the lateral incisors, the central incisors having been removed by trauma.

FIG. 2b.

been no miscarriages. No other cases of mental disease on either side of the family were known.

The boy was slow in development, being able to hold his head erect at 5 months and to sit unaided at 1 year. Walking was still not achieved when last seen at 2½ years. He was unable to feed himself, and was incontinent of urine and faeces. Since the age of 1 year he had been having 10 to 30 attacks of petit mal a day.

When the boy was examined, he had the appearance of a strong, healthy child with a normal facies not obviously suggesting mental defect. His hair was fair, eyes brown, and skin rough and dry with a pimply eruption on the extremities. The head was of normal shape and measured 18 inches in circumference, the fontanelles being closed. There were constant movements of the head and limbs, similar to those of a vigorous baby of 6 months of age and not suggestive of chorea or athetosis.

FIG. 3a.

FIG. 3a.—Case 3, at 10 years, showing dry eczematous patches, moles, and scratch marks on the trunk.

FIG. 3b.—Case 3, to show prominence of the maxilla.

FIG. 3b.

Concentration on interesting objects was transient, though vision was certainly present. There was no evidence of deafness, and all the other cranial nerves were normal. Although all deep reflexes were brisker than usual, there was no spasticity or weakness. An electroencephalogram showed spike-and-wave complexes typical of petit mal, but no other specific abnormality.

Case 2. John H. (Fig. 2), aged 6 years, the elder brother of the patient in Case 1, was much more severely defective. Born by normal delivery after a normal pregnancy, he was noticed to have a squint soon after birth, and when he was taken to hospital at 7 months old a diagnosis of probable mental defect was made. He began to sit up unaided at 3 years, crawled at 3½ to 4 years, and walked at 5½ years. He was completely incontinent, unable to feed himself, or to play with even simple toys.

When the boy was examined he presented the picture of gross mental defect, with complete lack of interest in the observer or in surrounding objects; there were purposeless, repetitive movements, sometimes of a self-destructive nature. The hair was light brown and the eyes grey-blue. There was some widening of the maxilla with spaced-out incisor teeth, though two had been lost by trauma. The skin was dry and coarse, and there were small pin-head papules over the elbows and knees. The skull was rather small, being 18¼ in. in circumference but of normal shape. Apart from the repetitive movements there were no other abnormal neurological signs.

While in the ward so that specimens of blood and urine might be collected, he lay or sat in bed, often in grotesque postures and frequently causing himself minor superficial injuries by his uncontrolled movements.

Case 3. Gwendoline W. (Fig. 3), aged 10 years, was born by normal delivery after a pregnancy complicated by mild toxaemia. She was premature and weighed 3¾ lb., but there were no severe setbacks in the early weeks.

The father and mother were of normal intelligence and unrelated. Both families had, however, lived in the same district in Norfolk for at least three generations. There were five children, of whom the patient was the third; the fourth child, a girl aged 4 years, was also a case of phenylketonuria (Case 4), but the others were of normal intelligence. There had been no miscarriages.

She had infantile eczema at 3 months. By the age

of 1 year she was noticed to be slightly abnormal: tensing and relaxing movements of the hands, and rolling of the head were observed. She sat unaided at 16 months, walked at 20 months, fed herself at 2 years, and by 3 years was able to fetch her mother ordinary household objects when asked. At the time of this examination, she was able to wash-up, mind the baby, and do other odd jobs in the house. Development of speech seemed to have lagged behind other functions, and she could say only a few single words, making herself understood mainly by gestures and unintelligible noises. She was clean in her habits, and only occasionally wet the bed at night.

She was a tall, thin child of fairly normal appearance, not obviously mentally defective. The maxilla was prominent, but the teeth were not widely spaced. The skull was of normal shape, and measured 20¼ in. in circumference; the hair was fair but becoming darker, and the eyes bluish-grey. The skin was dry and showed numerous scratch marks and many small pigmented moles. There was little or no repetitive movement, but she spent much time humming and singing tunelessly.

FIG. 4.—Case 4, at 4 years, showing the normal facies and good physique.

FIG. 5.—Case 5, at 23 months.

Walking was normal, except for slight clumsiness, and there were no abnormal neurological signs.

Case 4. Jennifer W. (Fig. 4), sister of Case 3, aged 4 years, was born by normal labour after a normal pregnancy. She was regarded as a normal healthy infant, and won two prizes at baby shows at the age of 6 months. She sat unaided at 11 months and walked at 1½ years. Having failed to talk by 2 years she was thought to be a little backward, and at 3 years her progress seemed to cease. Speech had not developed at the time of this examination, but she was able to indicate simple wants. She was incontinent of urine and faeces, and unable to feed herself. Her play was that of a child of about 18 months; for example, she tore up paper, and held dolls, but did not play intelligently with them. She was said to be good-natured and amenable.

She was a fair-haired child with blue-grey eyes, and her general appearance showed no signs of obvious mental defect. The skin, teeth, and jaws were normal, but the skull was brachycephalic, and the maximum circumference was 18¾ in. Apart from occasional outbursts of screaming and hyperactivity, there were no repetitive abnormal movements, and no abnormal neurological signs.

Case 5. Moira D. (Fig. 5), aged 18 months, was born by normal delivery after a normal pregnancy, and weighed 7 lb. 3 oz. Nothing abnormal was noticed in the newborn period.

The father and mother were of normal intelligence and not related. Both were of Irish parentage, but from

different districts. There was one brother aged 8½ years, a proven case of phenylketonuria living in an institution, and one sister aged 2½ of normal intelligence, with congenital dislocation of the hips. There had been no miscarriages. The girl's motor development had been slow; sitting without support was achieved by 13 months, and no attempt at walking had been made by the time of this examination. For the past six months frequent attacks of petit mal had occurred.

She was a fair-haired, blue-eyed child with constant, restless, incoordinated movements of limbs and trunk. The skull was of normal shape, measuring 18½ in. in circumference. The skin was dry, and numerous small papules were present on both forearms. The teeth were normally spaced and there was no enlargement of the maxilla. She was uninterested in her surroundings, and did not concentrate on objects presented to her, though she followed a light with her eyes for brief periods. Abnormal grunting sounds and grimaces were frequent, and limb movements were reminiscent of a baby of 6 to 9 months. Although deep reflexes were brisk and plantar reflexes extensor, no definite increase in muscle tone was present, and no other abnormal signs were found.

An electroencephalogram showed spike-and-wave activity typical of petit mal, but no other specific abnormality.

Further Investigations

Glutamic acid feeding is said to depress the blood level of other amino-acids (Christensen, Streicher, and Elbinger, 1948). In view of this fact, and of encouraging reports of treatment of mental defect with glutamic acid (Albert, Hoch, and Waelsch, 1946; Zimmerman, Burgemeister, and Putnam, 1947) including one case of phenylketonuria in France (Delay, Pichot, and Bertagna, 1949), it was decided to measure the effect of the administration of this substance upon the blood phenylalanine and daily output of phenylalanine, phenylpyruvic and phenyl-lactic acid in urine. It was thought that should an alteration in these values be found, it might help to establish a link between the biochemical disorder and the mental retardation. The blood level and 24-hour excretion of phenylalanine and its breakdown products were determined before and after one week of glutamic acid feeding (Table 1). The molecular weights of phenylalanine, phenylpyruvic acid, and phenyl-lactic acid are so close that simple addition is a valid method of arriving at the total of all three compounds (Table 1). In Case 1 treatment was interrupted, permitting two sets of results to be obtained.

Phenylpyruvic acid content was determined by a ferric chloride method (Woolf, 1949, unpublished). Phenylalanine and phenyl-lactic acid contents were determined by means of the Kapeller-Adler reaction (Jervis, Block, Bolling, and Kanze, 1940). The apparent phenylalanine given here includes phenacetylglutamine (Woolf, 1951).

The blood phenylalanine concentration does not seem to be much altered, certainly not consistently reduced, by the glutamic acid fed at these dosage levels. In all except one case the total of phenylalanine and its breakdown products excreted is markedly increased after glutamic acid feeding. This could be partially, but not completely, explained by its apparent diuretic effect.

All the urine and blood specimens were examined by paper chromatography (Consden, Gordon, and Martin, 1944) for amino acids. Apart from the large amount of phenylalanine in all specimens, other amino acids were normal before glutamic acid feeding. After glutamic acid feeding blood glutamic acid rose considerably, and glutamine in urine rose somewhat less markedly.

Since it was thought that if any benefit were to be derived from glutamic acid it would be most likely to occur in the youngest patients, Cases 1 and 5 were given long term treatment after developmental age was assessed as accurately as possible by Gesell's norms.

In Case 1 the developmental age was estimated at 9 months when the chronological age was 23 months. After five months treatment with L-glutamic acid ranging from 9 to 16 g. daily, a second assessment of developmental age was made, and an increase of only 4 to 6 weeks had occurred. After another six months of treatment there was little or no increase.

The second patient (Case 5) had a developmental age of about 8 months when she was 20 months old. After six months' treatment development was found to be no more than would be expected in a child with this degree of mental defect. Obviously, no definite conclusions can be drawn from two cases, but it seems unlikely that glutamic acid feeding, in a dosage which can easily be tolerated, produces the beneficial effect in phenylketonuria which was hoped for on theoretical grounds.

Comment

The relationship between the error in metabolism and the mental defect remains obscure. Other defects in intermediate metabolism of amino-acids, for example, alcaptonuria, do not have similar effects. It seems most probable that the phenylalanine, or one of its breakdown products, circulating in the blood in concentrations much higher than normal, depresses the activity of the higher mental centres.

If the amount of phenylalanine and its breakdown products could be reduced, normal cerebral function might result. Whether this would lead to recovery or not, would probably depend upon the duration of exposure of the brain to the injurious concentration of this substance.

Two possible methods of achieving this reduction seem worthy of investigation: restricting the phenylalanine intake in the diet to the basic minimum early in life; and increasing the rate of excretion of phenylalanine by administering a substance which would competitively reduce tubular reabsorption.

Summary

An account of the clinical and biochemical features of phenylketonuria is given and five cases

TABLE 1

MEASUREMENTS OF THE EXCRETION OF PHENYLALANINE AND ITS BREAKDOWN PRODUCTS BEFORE AND AFTER FEEDING GLUTAMIC ACID

Patient	Weight	Amount of Glutamic Acid (g./day)	Specimen	Volume	Phenylpyruvic Acid (mg./100 ml.)	Phenylalanine (mg./100 ml.)	Phenyl-lactic Acid (mg./100 ml.)	Total Excreted (mg./day)
Case 1 M.H.	29 lb. 3 oz.	0	Urine	360	97	87	118	1,089
			Plasma	—	—	31	—	
		9	Urine	470	81	117	86	1,335
			Plasma	—	—	39	—	
Case 1 M.H. 2	29 lb. 3 oz.	0	Urine	440	74	82	70	999
		9	Urine	560	113	68	84	1,485
			Serum	—	—	31	—	
Case 2 J.H.	41 lb.	0	Urine	554	74	112	169	1,963
			Serum	—	—	26	—	
		12	Urine	1,036	53	88	100	1,565
			Serum	—	—	21	—	
Case 3 G.W.	69 lb.	0	Urine	750	100	71	94	1,987
			Serum	—	—	21	—	
		30	Urine	875	100	80	68	2,370
			Serum	—	—	26	—	
Case 4 J.W.	36 lb. 4 oz.	0	Urine	410	79	38	98	881
			Serum	—	—	26	—	
		20	Urine	605	75	52	80	1,252
			Serum	—	—	25	—	

are described, in two of which the patients were aged only 18 months.

Contrary to expectation, no alteration in blood phenylalanine was found to occur after administration of glutamic acid, though the total amount of phenylalanine and its breakdown products excreted in the urine was found to increase in all except one case.

No significant increase in intelligence was found after continued administration of glutamic acid in the two patients treated.

Addendum

Since this report was written it has been found that phenylpyruvic acid is partially broken down *in vivo* to phenylacetic acid and this is excreted conjugated with glutamine (Woolf, 1951). The excretion of conjugated phenylacetic acid by phenylketonuric patients is much higher than that of normal individuals, with the exception of a single case of phenylketonuria examined through the courtesy of Dr. B. H. Kirman. This patient (John R.) excretes a normal amount of conjugated phenylacetic acid and is also exceptional in having an intelligence quotient as high as 97 (Cowie, 1951). The phenylalanine content of his blood and urine are as high as is usual for these patients, and he excretes large amounts of phenylpyruvic acid. On the other hand, the most severely affected phenylketonuric idiot examined, with a social quotient of 3, excretes more conjugated phenylacetic acid than any other patient examined. This suggests that the intellectual defect is due to an intoxication by phenylacetic acid. The condition might be curable if the *in vivo* conversion of phenylpyruvic acid to phenylacetic acid could be prevented.

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THE SIGNIFICANCE OF BRUSHFIELD'S SPOTS IN THE DIAGNOSIS OF MONGOLISM IN INFANCY*

BY

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(RECEIVED FOR PUBLICATION JANUARY 11, 1951)

The diagnosis of mongolism in infancy is often difficult. Benda (1947) suggests that the incidence is between 2 and 3 per 1,000 live births or possibly higher. The rate over 14 years at Boston Lying-in Hospital was 3·4 per 1,000. Most British observers are incredulous of this figure which may be an indication of a different rate of incidence in this country, or of the fact that mongolism is sometimes not diagnosed until later in life here. The mortality among mongols is very high especially in infancy, and it may be that many of them die without having been recognized as mongols. A survey of the published work indicates that the difficulty of diagnosis at an early age is well recognized. It also gives some clues to a possible diagnostic sign.

Historical

Langdon Down (1866) is usually credited with the first description of mongolism. Ruhräh (1935) considers on slender evidence that a painting by Andrea Mantegna (1431-1506) includes a portrait of a mongol child. Shuttleworth (1909) and Brousseau (1928) suggest that Seguin in his writings (1846, 1866) was referring to mongols when he described 'furfuraceous cretins.' Benda (1947) quotes from Seguin's book, *Idiocy and its Treatment by the Physiological Method* (1866) the following:

> 'Furfuraceous cretinism with its milk-white rosy and peeling skin ; with its shortcomings of all the integuments, which give an unfinished aspect to the truncated fingers and nose; with its cracked lips and tongue, with its red ectropic conjunctiva, coming out to supply the curtailed skin at the margin of the lids.'

Benda calls this a precise description of the type, but most readers will agree with him when he speaks later of 'Langdon Down's classic paper on ethnic classification of idiots in which mongolism was described for the first time.'

During the next 50 years the diagnosis of mongolism received much attention and many of its characteristic features were described.

Mitchell (1876) stated that in a large proportion of cases these idiots were recognized as notably small and weak at birth. He considered that the condition dated from intra-uterine life.

Telford Smith (1896) described the mongol hand, noting particularly the incurved little finger, which he found in 'nearly every case.' For some time this was known as 'Telford Smith's sign.'

Still (1898) emphasized the microcephaly and dwarfism, with late closure of the fontanelles. He noted the large rough tongue and the epicanthic fold, and described a habit of looking out of the corners of the eyes in a sly way.

Thomson (1898) said that the condition can be diagnosed even at the time of birth and added: 'In most cases the axes of the palpebral fissures are abnormally oblique. In a large proportion also there is a marked development of the so-called epicanthic fold of skin at the inner angle of the eye.' In 1907 he pointed out that though the tongue is swollen at birth, the roughness and enlargement of the papillae appear later (at 3 to 9 months), and the fissuring after the second year. He considered that these features were acquired through the habit of sucking the tongue.

Bourneville (1901) noted persistence of the frontal suture in all mongols. He found this also in 8% of normal white people. Hill (1908) reported a case with congenital cataract. In 1909, Langdon Down's son, R. L. Langdon Down, described abnormalities in the fold-lines on the palm of the hand, namely that there are two instead of three main ones. Shuttleworth (1909) mentioned the advanced age of the mother at the birth of the child.

Pearce, Rankine, and Ormond (1910), dealing with the ocular condition, reported cataract of the lamellar or congenital dot type in 18 out of 28 cases. They stated that very young mongols did not

* Based on a thesis for the degree of M.D. (Cantab.).

exhibit this change, though the youngest of their reported cases was 5 years old.

By this time it was becoming evident that the features of mongolism are variable, and that no single one of them can be considered absolutely diagnostic. West (1901) showed that 'Telford Smith's sign' was present in 33% of normal children (605 cases), and absent from two of nine mongols he had seen. Fennell (1904) found an epicanthic fold in eight only among 23 mongols. He found the palpebral fissures to be horizontal in three cases and slanting downwards and outwards in one case.

Tredgold (1908) said:

> 'It is necessary to remember that mongolism consists in a particular *combination* of anomalies rather than in anomalies which are distinctive in themselves; and there are many ordinary aments who possess one or more of the features which go to make up the *tout ensemble* of the mongol; in fact I do not know of any single feature of these persons (with the possible exception of the tongue), which may not be seen in other aments.'

Even so, in 1917 Weber gave an example of what may happen if one or even two isolated signs should be considered as diagnostic of the condition:

> 'Mongolism need not, of course, necessarily, be associated with idiocy or imbecility. Thus G. A. Sutherland (*Rep. Soc. Stud. Dis. Ch.*, 1907, vii, 100), showed a girl aged 8 years with shortening and curving of the little fingers, as in the present case, and with the oblique or slanting palpebral fissures, characteristic of the mongoloid type of imbecility but she was perfectly intelligent.'

In 1924 Thomas Brushfield, in his thesis for the degree of Doctor of Medicine of Cambridge University, gave an excellent description. He studied 177 cases aged from 2 to 10 years. He stated that the diagnosis had often been made at birth, and noted that the anterior fontanelle closed late. All his cases had strabismus, and 40% had epicanthic folds. Cataract was found in three cases, but the eyes were not examined for the 'dot cataract.' Of the iris he said:

> 'The following varieties of iris were observed. (1) mottled or marbled iris; (2) speckled . . . white or very light yellow clearly defined pin-points near the outer margin, generally placed at regular intervals in a ring and appearing to be placed on the iris. I have not been able to find these in the brown iris.'

Crookshank (1924) stated: 'the normal hand has two or three transverse lines; the mongolian imbecile and the orang-utan only one.' Herrman (1925) stated that he saw 40 cases and found a single transverse line in only 10. In seven of these the abnormality was on one hand only. He also stated that the epicanthic fold is present in all infant mongols, but disappears in about 50% of cases as they grow older.

Stewart (1926) observed that 'the colour of the iris varies although blue-eyed mongols appear to predominate in this country. When blue, the iris often shows a curious speckled arrangement of the pigment to which Langdon Down first drew attention.'

Brousseau (1928) dealt with the subject exhaustively, and gave references to 467 original works. She omitted the important reference to Brushfield's paper, though that is easily available, as it was printed in the *British Journal of Children's Diseases*. She said:

> 'No abnormality has been discovered that is peculiar to mongolism, and that would therefore give some indication of the cause of the disorder. It is a combination of several anomalies rather than the presence of any one of them that distinguishes the type.'

In 1933 Penrose stated: 'the iris often shows a curious speckled arrangement of the anterior yellow pigment to which Langdon Down first drew attention.' Penrose listed seven characters: (1) an intelligence quotient between 15 and 29; (2) a cephalic index of 0·83 or more; (3) epicanthic fold; (4) fissured tongue; (5) conjunctivitis; (6) transverse palmar line on either hand; and (7) one crease only on the minimal digit of either hand.

He found that almost three-quarters of the mongols have three or more of these characters, but only six out of 350 other unselected mental defectives have three or more. Any defective with four or more of these characters is almost certainly a mongol.

Benda (1939) considered that the previous discrepancies were due to investigators studying the disease at different ages. For instance the skull is normal in size at birth, but becomes microcephalic after six months; and the height is at the lower limit of normal for six years and after that small for the age.

In 1944 Tredgold reiterated his opinion:

> 'Although the great majority of mongols are easily recognized, there are many defectives who are not mongols but who present some of the features of this condition, and these are known as "semi-mongols." In fact there is hardly a single feature of mongolism which I have not seen in ordinary defectives, and some of them are found in normal persons.'

Recently attention has been paid to the palm-prints and finger-prints of mongols (Cummins, Keith, Midlo, Montgomery, H. H. Wilder, I. W. Wilder, 1929; Cummins, 1936 and 1939; and Penrose, 1949). Cummins (1939) reported 'departures from the normal which are to be

regarded as stigmata of mongolism'; but he also stated: 'It must be remembered that as in other constitutional and racial expressions of dermatoglyphic variation the distinctions appear as trends characterizing the group rather than in the occurrence of traits which are diagnostic of the individual case.' Penrose (1950) states that the palm-prints of mongols are highly specific, but there is some overlapping with normal types.

Lowe (1949) described the mongol eye in detail. Of the iris he says (Figs. 1 and 2):

> 'The speckling . . . is sometimes seen in normal people. It is . . . very uncommon in association with other than blue irides. In young mongoloids just beyond the region where the stroma pigment suddenly becomes thinner, the strands tend to bunch at almost regular intervals around a circle concentric with the pupil; where these strands run together pigment collects or the strands remain thicker, thus presenting an appearance of small golden or white splashes.
>
> This speckling was found in 56 patients in the present series (nearly 90%). Its appearance has been noted by previous observers, and it is considered a characteristic of mongolism. When the eyes are moist it gives a most attractive appearance to shining blue eyes.'

An example of these spots is shown in Figs. 1 and 2.

All children of British race have blue eyes at birth. It seemed, therefore, that it would be of value to investigate a series of infant mongols and determine whether they all had blue irides, and, if so, whether all without exception had spots on the iris.

Investigation

The newborn babies in the large modern maternity block of a municipal hospital were observed for a period of nine months. Approximately 2,250 births occurred, and five mongol children were detected. These five were studied in detail, and seen at intervals up to two years after birth. Two other mongols (Cases 6 and 7) under the age of 1 year, were also examined.

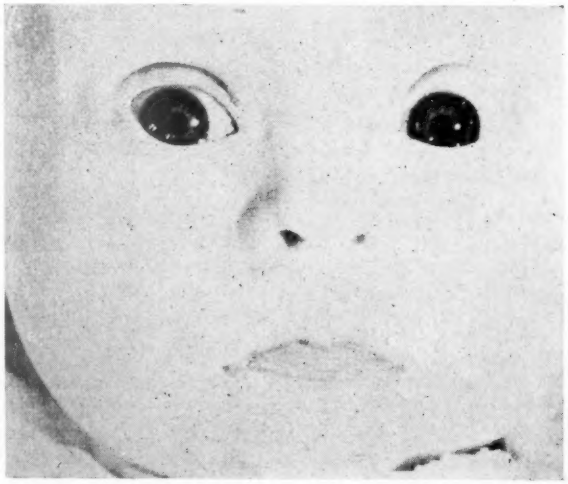

FIG. 1.—The specks are seen best on the left eye arranged in a circle at the junction of the outer and middle thirds of the iris.

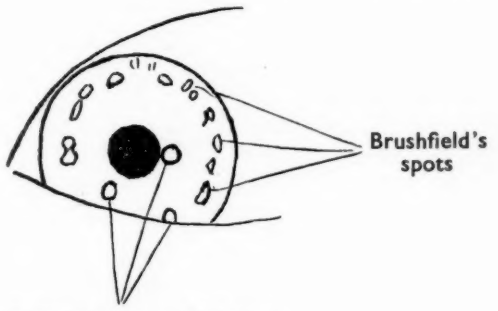

FIG. 2—Detail of the left eye.

Attention was directed particularly to the irides, with a view to solving the following problems. (1) Are the spots on the iris confined to mongols? (2) Are they present in all newborn mongols? (3) If so, do they disappear if the iris changes colour from blue to brown or hazel?

The general findings are summarized in Table 1 and those concerning the irides in Table 2. Three cases (8, 9, and 10), are included as controls. They were not mongols though they had speckled irides.

The general findings confirm what other workers have found. The mortality rate was very high. The birth weights and head measurements were on the low side of normal. The sutures were more widely open than normal in five cases out of six seen in the first month of life. Other features showed the usual variability. Apart from the irides there was no constant feature: even the tongue was normal in one case.

One child was found to have a dot cataract within a month of birth. Most authors state that this type of cataract does not occur in very young mongols. None of them, however, record evidence of having examined mongols in infancy. It may be that those mongols who have dot cataracts in infancy do not survive to an age at which ophthalmologists begin to study them. This one died at 2 months.

One child had a congenital skin defect, and another suffered from thrombosis of the cerebral veins, due possibly to external version at the seventh month of pregnancy.

The Iris. Investigation of the irides, summarized in Table 2, gave the answers to the three problems.

Spots were seen in infants who appeared to be

TABLE 1
GENERAL FINDINGS REGARDING MONGOLISM IN INFANCY

Case No.	Age		Birth Weight		Head Circumference (in.)	Sutures	Palpebral Fissures	Epicanthic Fold	Tongue	Ears
Mongols	M.	F.	Lb.	Oz.						
1	38	40	5	14	13¼	Open	Oblique	Present	Normal	Abnormal
2	37	40	7	0½	12½	Open	Oblique	Present	Large	Abnormal
3	36	36	3	13	11½	Open	Oblique	Present	Large	Abnormal
4	40	42	7	8	12¾	Open	Normal	Absent	Large	Abnormal
5	31	35	6	5	12½	Normal	Oblique	Absent	Large	Normal
6	28	29	6	2	14¾ at 8 months	Normal	Oblique	Absent	Large	Normal
7	35	36	7	9	15¼ at 21 days	Open	Oblique	Present	Large	Normal
Controls										
8	26	30	7	15	13¾	Normal	Normal	Absent	Normal	Normal
9	22	23	6	4	13½	Normal	Normal	Absent	Normal	Normal
10	27	30	7	0	17 at 8 months	Open	Normal	Absent	Normal	Normal

normal, and were developing normally later in childhood. They have also been observed in normal adults.

In this series of cases all newborn mongols were found to have blue irides with white spots. This is an observation which has not previously been reported. The number of cases is small, and further search is needed.

Case 5 suggests that the answer to the third problem is yes. The baby was seen within a week of birth, and the irides were blue with white specks. At 2 years the irides were brown, and no spots were visible. This is another phenomenon which has not previously been reported. It is thought that this might be the usual course with brown-eyed mongols.

Previous authors have agreed that there is no single constant sign of mongolism. This investigation shows, however, that there is one: speckled blue irides in infancy. Unfortunately normal children may exhibit the same sign. One cannot say, 'This baby has speckled irides, therefore it is a mongol.'

The First Description and Suggested Nomenclature

It is interesting to note that both Stewart (1926) and Penrose (1949) attribute the first description of the spots to Langdon Down. But a search of the published works of J. Langdon Down (1866, 1887, and 1892) and R. L. Langdon Down (1906 and 1909), and of many other workers not included in the list of references below, does not reveal a description of the spots earlier than that given by Brushfield in 1924. Brousseau (1928), despite her 467 references, gives no help in this matter. A standard textbook of ophthalmology (Duke-Elder, 1938) makes no mention of them, but a neurological work (Wilson, 1940) has a description and a picture.

In answer to an inquiry Dr. Stewart wrote in 1947:

> 'I am afraid I gave Langdon Down the credit of having first noted the speckled iris of the blue eyed mongol when it should have gone to Brushfield. I can remember that it was the late S. A. K. Wilson who first called my attention to it, and when I asked him how Brushfield had found it out he said he thought it was from Langdon Down's description. I believe that is all I can tell you about it except that this condition can, of course, be found in the perfectly normal subject.'

Professor Penrose wrote (1947):

> 'I am sorry to have been the unwilling cause of your wild goose chase after Langdon Down and speckled irides. If there is no mention of this in

TABLE 1 (*cont.*)

Fingers	Palm Creases	Toes	Heart	Other Abnormality	Follow-Up
Abnormal	1R 1L	Normal	Normal	Nil	Seen at one year
Abnormal	1R 2L	Abnormal	Normal	Nil	Died 4 months (No necropsy)
Abnormal	1R 1L	Normal	Normal	Premature	Died 4 months (No necropsy)
Abnormal	2R 1L	Abnormal	Murmur	Congenital skin defect Atelectasis	Died 6 days (Necropsy refused)
Abnormal	2R 2L	Normal	Normal	Nil	Seen at 2 years
Abnormal	1R 1L	Normal	Murmur	Nil	Went abroad
Abnormal	1R 1L	Abnormal	Patent foramen ovale	Thrombosis of cerebral veins	Died 7 weeks (Necropsy performed)
Normal	2R 2L	Normal	Normal	Nil	Seen at 2 years
Abnormal	2R 2L	Normal	Normal	Nil	Seen at 19 months
Normal	2R 2L	Normal	Normal	Syringo-myelocele	Died 9 months

the *London Hospital Report* for 1866, probably my belief that L. Down first noticed these spots is erroneous. I cannot remember now where I got the idea but it is possible that Brushfield may have told me so in conversation.'

Dr. Brushfield was medical superintendent of the Fountain Hospital for Imbeciles, Tooting, from 1914 to 1927. He died on May 17, 1937, at the age of 79. Neither *The Lancet* nor the *British Medical Journal* printed an obituary tribute. In 1930 he deposited his papers in the library of the Royal College of Surgeons in London. These papers have been studied. They were very dusty, but did not serve to elucidate the point further. There was no more information about the spots than is given in his thesis, and no reference to any prior description.

The evidence which has been presented proves that he was the first to describe the speckled iris in mongolism. The use of eponyms in medicine has been discouraged recently. But their use adds to bare facts a pride in history. Moreover they are in many cases very convenient if not indispensable. It is suggested that these spots on the iris, so constant in infant mongols, should go by the name of the English physician who first described them, and be called ' Brushfield's spots.'

TABLE 2
FINDINGS REGARDING IRIDES

	Case No.	Iris at Birth	Follow-up	Iris Later
Mongols	1	Blue speckled	One year	Blue speckled
	2	Blue speckled	Died	—
	3	Blue speckled	Died	—
	4	Blue speckled	Died	—
	5	Blue speckled	Two years	Brown, not speckled
	6	Not seen	First seen at 8 months	Blue speckled
	7	Not seen	Died	Blue speckled at 21 days
Controls	8	Blue speckled	Two years	Blue speckled
	9	Blue speckled	19 months	Blue-grey speckled
	10	Not seen	First seen at 8 months	Blue speckled

Summary

The published work on mongolism has been studied with particular reference to the possibility of diagnosis in early infancy. Most authors agree that although diagnosis is possible at birth, there is no single constant sign.

A series of infant mongols has been observed and it has been found that all have blue eyes with white spots on the irides. These spots disappear if the colour of the iris changes to brown as the child grows older. The spots are seen in some normal children also, and their diagnostic value is not great except in a negative sense.

The first description of the spots had previously been attributed to Langdon Down, but it has been proved that the credit should go to Dr. Thomas Brushfield. It is now suggested that they should be known by his name.

I wish to thank Dr. R. M. Stewart and Professor L. S. Penrose for permission to quote from their personal communications, and Dr. J. Apley for the photograph.

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EPILEPSY IN MONGOLISM

BY

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It is generally agreed that epilepsy is rare in mongolism. Penrose (1949) states that it is no more common in mongolism than in the general population. The older authors (Ireland, 1877 and 1898; Barr, 1904; Kelynack, 1915) do not mention epilepsy in mongolism, nor does Benda (1947) in his extensive review of the subject. This is surprising in view of the frequency of epilepsy among other groups of imbeciles. It is, however, in keeping with the absence of evidence of focal lesions in the brains of most mongolian imbeciles. Engler (1949), it is true, mentions that 8·85% of his cases were epileptics, but it would appear that his experience is unusual; compare his statement that after many years' experience he has seen only one mongol with red hair. Of 91 patients with mongolian imbecility at the Fountain Hospital only one had fits.

Case Report

The baby, a boy, was born on November 1, 1939. The family history showed that there was no history of fits or mental deficiency in any member of the family. The father was 41 and the mother was 43 at the time of the child's birth. The father is a tailor. The mother suffered from a broken leg during pregnancy. In 1945 she was suffering from leukaemia.

The siblings in the family are shown in Table 1.

TABLE 1

SIBLINGS IN FAMILY

	Sex	Age (1945)	Comments
1.	M		Stillborn about 1922
2.	M	22	Healthy, married
3.	F	17	,, at home
4.	F	14	,, scholarship
5.	M	5	Patient

The patient's previous history showed that the confinement was very difficult, and the child is said nearly to have died. Mental deficiency was noted at an early age: mongolism and congenital abnormality of the heart were diagnosed. In April, 1942, the child was said to have had a cerebral haemorrhage, followed by left hemiplegia. He became suddenly ill, was comatose for two days, and six days later it was noted that one eye was closed and the left arm and leg were held still.

When he was admitted to hospital on August 15, 1945, he did not know his name. He could say only a few single words. He did not grasp objects put into his hand, and did not obey simple commands. He did not play with toys. He was incontinent of urine and faeces. He could not stand, walk, or use a spoon. He showed little interest in his surroundings.

He had the typical features of mongolism. The head measurements were: length 6¼ in., breadth 5½ in. (cranial index 0·88), circumference 19¼ in. He was somewhat pigeon-chested. There were a few râles in the left chest and a harsh murmur in the pulmonary area. He had a left spastic hemiplegia. The right side showed the hypotonus usual in mongolism, and he could put the foot behind his head with ease. There was well marked finger clubbing. The Wassermann and Meinicke reactions were negative.

It was noted soon after admission that he was delicate. He developed enteritis, stomatitis, and later bronchitis, becoming very cyanosed. Bronchitis persisted with occasional low pyrexia. On one occasion in 1946, he became deeply cyanosed and collapsed. The cyanosis persisted with varying intensity until his death. The finger clubbing increased and the toes were also markedly affected. In 1947 the abdomen was found to be grossly distended, though free fluid was not detected. At that time he had learnt to feed himself and to obey simple commands. He was friendly and usually was clean in his habits.

Epileptic fits began in 1948, seven months before his death. They were major generalized attacks, each of which perceptibly increased the circulatory embarrassment. A total of 29 occurred.

In June, 1948, gross oedema of the legs appeared. It was thought that ascites and enlargement of the liver were present. In September of the same year he became more cyanosed and distressed, finally collapsing and dying.

At necropsy it was found that the body was that of a well nourished boy with marked 'mongol' features. There was pronounced cyanosis especially of the face and mucous membranes. Finger clubbing was extreme. All the abdominal organs showed congestive changes.

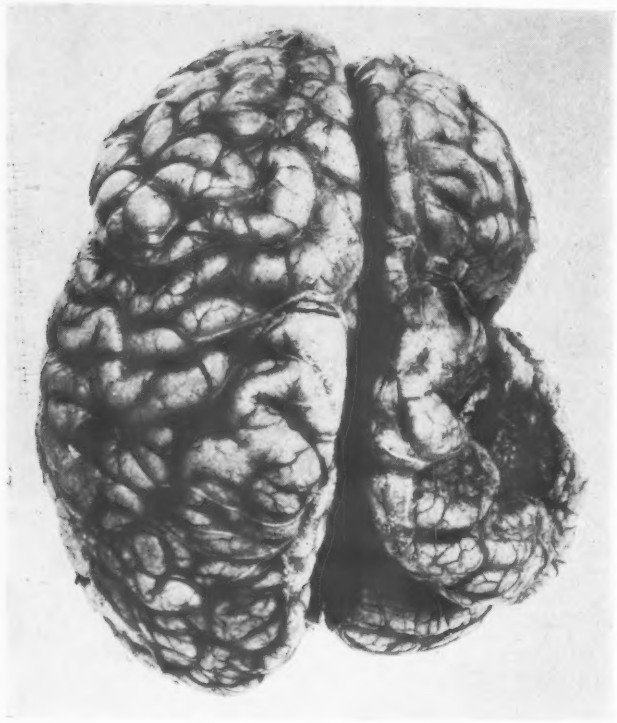

FIG. 1.

FIG. 1.—View of brain from above showing the right cerebral hemisphere, shorter and narrower than the left with a large irregular dark sunken defect.

FIG. 2.

FIG. 2.—View of the brain from below. The right internal and middle cerebral arteries are markedly narrower, probably as a result of occlusion of the internal carotid artery by an embolus or thrombus in the past. The floors and walls of the widened lateral fissure represent the lower boundary of the cerebral defect, and are covered by thickened meninges. On the side opposite to this lesion the left cerebellar hemisphere is smaller than its fellow.

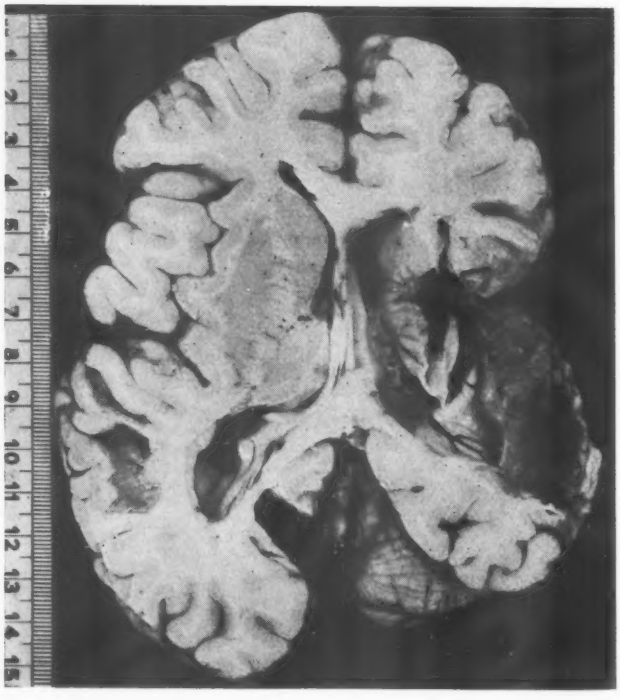

FIG. 3.

FIG. 3.—Cerebrum sectioned horizontally. All the tissue lateral and medial to the right lateral ventricle is reduced to a membrane only 1 mm. thick in places. The caudate nucleus survives, but is much smaller than on the opposite side. The lentiform nucleus, thalamus, and internal capsule are absent or rudimentary.

The left kidney was extremely small and the right correspondingly hypertrophied. The lungs were also markedly congested. The heart was enlarged and showed Fallot's tetralogy. The right ventricle occupied more of the anterior surface than is usual. Both atria were distended. There was virtually only one auricular cavity, the septum being represented by only a few fibrous strands. The interventricular septum was also grossly defective, with an opening 35 mm. wide. The tricuspid and mitral valves were not differentiated. There was pulmonary stenosis, the pulmonary artery being only 5 mm. wide at its origin. The pulmonary valves were absent.

The meninges participated in the general congestion. There was atrophy of the right cerebral hemisphere, especially in the anterior part of the parietal lobe adjacent to the Sylvian fissure.

Commentary

In view of the history and pathology in this case there is little doubt that the unusually severe degree of heart defect led to a cerebral vascular catastrophe and that the epilepsy was a sequel to this and was not due to the cerebral abnormalities of mongolism. The surprising thing about the case is that with such a grossly inefficient heart it was possible for the nursing staff to keep him alive for so long. It will be noted that the fits did not start immediately after the development of the hemiplegia but began only a few months before death. It seems probable that the rapidly failing circulation with consequent cerebral congestion and anoxia contributed to the development of epilepsy.

It was customary not long ago (Tredgold, 1929; Brain, 1947) to divide both mental defect and epilepsy into 'primary' and 'secondary'. (The terms ' idiopathic ' and ' symptomatic ' are used of epilepsy.) These terms are without value and in fact misleading. Bateman (1936) studied the brains of 178 epileptics and found only two normal. It is true that other workers have found a lower proportion of gross anomalies. It is clear that a study of a similar series of brains from cases of gross mental defect would have similar results, though unfortunately no such examination has yet been carried out on an adequate scale (despite the work of Ashby and Stewart, 1933, 1934, 1935, in limited areas of this field). Since the imbeciles and idiots on the one hand and epileptics on the other, have in common a localized abnormality of the brain in a majority of cases, it is not surprising that many imbeciles and idiots should be epileptics and vice versa. The peculiar feature of the group of mongolian imbeciles, who form some 10% of the population of this hospital, and more in the younger age groups, is the extreme diffuseness of the cerebral lesion and the general retardation of the growth of the brain. A special feature is the relative smallness of the cerebellum and the brain stem. This may be related to the low muscular tone and acrobatic potentialities of the ' mongol ' and may also be significant in relation to his immunity from epilepsy.

Apart from its relationship to more general problems the absence of epilepsy in mongolism is of practical importance since it is connected with the relative tractability of this group and does something to offset their generally low level of occupational attainment.

My thanks are due to Dr. M. K. Beattie for the necropsy report, to Dr. M. C. H. Dodgson for the report on the brain, and to Mr. J. E. Stevens for the photographs.

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THE ORIGIN OF LUNG CYSTS IN CHILDHOOD

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Since the early description of a lung cyst by Fontanus in 1638, many authors have thought these cases worthy of record, and their aetiology has often been the subject of speculation and controversy. Occasionally the indisputable evidence of a congenital origin is provided at necropsy on a stillborn foetus, but more often the authors' conclusion as to whether the disease is congenital or acquired is based on embryological and histological data supported by a wealth of conjecture. The purpose of this paper is to present a group of cases in which further light is shed on the development of lung cysts by prolonged clinical observation and serial radiography, and to develop the concept that in most of these cases the disease is acquired rather than congenital.

Congenital Theory

The frequent finding of pulmonary cysts in young children is not enough to establish a developmental origin, and the arguments in favour of this aetiology rest on the occasional observation of similar cysts in the foetus, their occurrence in association with other structural anomalies, the finding of abnormal histological patterns unlikely to have resulted from an acquired cause, and on the opinion of knowledgeable pathologists who have made a detailed study of individual cases. The literature supporting a congenital origin of lung cysts will be reviewed before passing on to argue how such cysts could have developed in postnatal life.

The cyst of the lung described by Fontanus was found in an infant 3 months old. Bartholinus (1687) mentioned a child of 4 years with cystic dilatations in the left upper lobe. In the last century many congenital lung cysts were reported by Meyer (1859), Biermer (1860), and Barlow (1880). Grawitz (1880) reported the case of an infant 5½ months old who showed epithelial-lined cysts throughout both lungs which did not communicate with bronchi. There was an excess of cartilage in the cyst walls and a complete lack of fibrous tissue. Löhlein (1908) observed epithelial and connective tissue hyperplasia, and suggested that the cysts were neoplastic foetal adenomata. This view had also been held by Couvelaire (1904) who found in the large middle lobe of an infant of 6 days old multiple small fluid cysts lined by cuboidal or columnar epithelium and surrounded by alveoli of normal appearance. Hueter (1914) thought arrest in bronchial development was the cause of lung cysts, because the spongy lobe he observed in a stillborn child was filled with acini lined by low cuboidal epithelium, but no bronchi entered the part. Virchow (1862), and Klebs (1889) argued that multiple cysts were anomalous lymphatic dilatations similar to those seen in other parts of the body such as the kidney. Klebs was of the opinion that there were many more cysts than could be accounted for by bronchial dilatation. Balzer and Grandhomme (1886) produced evidence that bronchiectasis and cyst formation were common in congenital syphilis. Sauerbruch (1934) considered that part of the developing left bronchial tree may be constricted by pressure of the heart or by the duct of Cuvier and that, depending on the stage of development at which the stricture occurred, these isolated parts became large cysts, multiple grape-like cavities, or bronchiectasis of medium bronchi.

Most of the earlier writers on cysts in the lung did not distinguish between solitary or multiple round cysts and the lesser degrees of bronchial dilatation which are now called bronchiectasis. Laennec (1821) described cases of dilatation of the bronchi in which there were marked inflammatory changes and a history of chronic pulmonary infection. The view that bronchiectasis is an acquired condition has now almost entirely replaced the congenital hypothesis, and has resulted in the absurd popular assumption that bronchial dilatations from cylindrical to gross saccular are of acquired origin, but the slightly greater degree in round cysts

is assumed to be caused by developmental malformation. In 1933 Kartagener recorded the extraordinary frequency with which transposition of the viscera is associated with bronchiectasis. Both these conditions are rare, yet a quarter of the former have bronchial dilatations, and the frequent co-existence of these features has been confirmed by Adams and Churchill (1937) and Olsen (1943). Other authors have shown a familial incidence of this association, Torgersen (1946) and López Areal (1944), and it has been claimed that transposition of the viscera is inherited as a rare recessive character (Cockayne, 1938). Because bronchiectasis occurs so often in patients with this congenital anomaly, it has been suggested that the bronchial dilatation also has a developmental origin. With regard to this last point, it is interesting to note that very few cases with situs inversus totalis show the type of solitary pulmonary cyst or polycystic lung disease which is generally regarded as congenital. Andrews (1949) recorded a recent example of the latter in which there was dextrocardia and cysts in the left upper lobe.

There will be no discussion in this paper of the round opacity in the chest which may be produced by a fibroma, lipoma, nerve tumour, secondary malignant growth, hydatid cyst, cyst of gastric epithelium, or loculated interlobar effusion; nor will mention be made of the spurious air-containing lung cyst suggested by an eventration of diaphragm, diaphragmatic hernia or small pneumothorax. Supernumerary lung lobes and sequestered pulmonary tissue outside the lung are germane to this study and frequently contain cavities. A supernumerary lobe, when well demarcated, can be confused with a lung cyst, particularly an azygos lobe in the upper chest or the rare caval lobe in the lower. Ruge (1878) described a small accessory lobe receiving its blood supply from an intercostal artery, and Humphry (1885) another which was attached by a narrow pedicle to the descending aorta. Muus (1904) and Linser (1899) have reported intrathoracic collections of cystic aberrant lung tissue with no connexion with the rest of the pulmonary parenchyma, and Vogel (1899) and Seltsam (1905) found an accessory lung lobe the size of the spleen under the left leaf of the diaphragm. Misplaced pulmonary cysts lined by bronchial epithelium are more often located in the mediastinum about the bifurcation of the trachea (Gold, 1921; Carlson, 1943; Brown and Robbins, 1944; Allison, 1947). These cysts are usually filled with fluid, but some have a bronchial connexion with the trachea or main bronchial stem and contain air. Cystic pulmonary tissue lined by ciliated columnar epithelium has even been found embedded in the liver (Friedreich, 1857; Zahn, 1896).

Congenital sequestration of lung tissue can also be intralobar, as has been pointed out by Pryce, Holmes Sellors, and Blair (1947). This consists of an ectopic pulmonary mass with usually a blind bronchus and abnormal arterial supply situated in one of the lower lobes. The condition is clearly developmental, the tissue is often cystic or bronchiectatic, carbon pigmentation is generally lacking, and the whole is apparently due to the fact that a portion of the developing lung acquired in very early life a blood supply from one of the dorsal aortae instead of from the ventral aorta or pulmonary artery. Though the main arterial supply to such sequestrated pulmonary tissue arises from the aorta, the artery itself is usually an elastic structure resembling a pulmonary rather than a systemic artery.

Lung cysts have been reported in patients of all ages. They may occur throughout both lungs, but are usually confined to one side and frequently to one lobe. One, or perhaps a collection of three or four cysts, may be visible radiologically. Others, being too crowded together or too small, may not be visualized radiologically, though in the macroscopic specimen they are obvious, and sometimes appear as a honeycomb of multiple small cysts filled with glairy fluid or air. Microscopy reveals columnar ciliated bronchial epithelium in the cyst wall, though it may be cuboidal if there has been much distension, and after infection squamous metaplasia can occur, or almost total denudation of the mucosa. Outside the epithelium, normal elastic and muscle tissue may be found, but sometimes a variable amount of fibrous connective tissue is seen with bronchial wall elements, such as cartilage, glands, and smooth muscle arranged irregularly. In a number no normally developed terminal respiratory units can be found about the cystic lung segments. The albuminous fluid material in uninfected cysts is composed of mucus and cellular debris. The morbid specimen, in patients who have lived for more than a few years, fails to show lung pigmentation in the cystic area, though it is present in the rest of the parenchyma and confirms the view that the cysts are congenital, or arise in very early infancy.

The bronchial tree develops with the trachea from undifferentiated mesenchyme enclosed in the primitive branchial arches. As the foetus grows, this tissue descends into the thorax and spreads out on either side as the primitive lung bud. The heart and great vessels are also derived from mesenchyme enclosed by the branchial arches and descend into the thorax in front of the endodermal tube, which will later divide into two to constitute the oesophagus and trachea. The bronchial tree develops as small

ramifications of solid endodermal tissue which become canalized almost immediately. In developmental or congenital cystic disease of the lungs an unknown process is thought to interfere with canalization at some point proximal to the termination of the bud; distal to this point canalization begins again, producing an isolated canalized segment lined by normal bronchial mucous membrane. The mucosa and glands assume their normal secretory function, but when fluid is secreted faster than it can be absorbed, or drainage into the lymphatics and blood stream is imperfect, the material accumulates and a fluid cyst is formed. The lung enlarges enormously after birth, and a few air cysts result from rupture of fluid cysts into the bronchial system and replacement of their contents by air. The majority of congenital air cysts are due to tremendous distension of some bronchi by a raised air pressure beyond a developmental stenosis or check valve formed by redundant epithelium; such distension occurs because of a congenital weakness in the bronchial wall or failure in development of the supporting parenchyma. The enlargement of air-containing cysts is favoured by a negative intrapleural pressure and widening of the bronchi on inspiration. The narrow ostia connecting some cysts with patent bronchi are situated tangentially on the circumference of the cysts, and assume what the French refer to as a *bec de flute* appearance. These may act as check valves by allowing the entrance of air on inspiration and preventing its escape through compression of the opening during expiration. Infection is frequent in pulmonary cysts because of the stagnation of secretions within them, and in nearby bronchi partially occluded by swelling of the cysts. When there is no stenosis of the ostia connecting cysts to bronchi, and secretions from the cysts can drain away easily, the presence of cystic disease of the lungs may not be diagnosed until some episode occurs in later life, such as a haemoptysis or infection, which brings the condition to light. Congenital lung cysts are generally classified as simple or multiple, fluid or air-containing and, according to whether the bronchial opening is closed, open, or valvular.

The literature on ' congenital ' cysts of the lung has been extensively surveyed by Koontz (1925) and Schenck (1937). The latter recorded the site and type of all the congenital cystic lungs described up to 1937, together with the age when they were recognized, and the chief symptoms of the patient. Altogether there were 374 cases in which the type of cyst was mentioned. They are tabulated below.

Lung cysts with a wall structure characteristic of bronchial tissue have been found at necropsy in stillborn foetuses, as reported by Meyer (1859), Hondo (1904), Hammar (1904), Zipkin (1907), Smith (1925), and Wolman (1930). Wolman's case was a premature baby of six months' gestation. The large right lung was full of cysts, and displaced the mediastinum and heart into the left hemithorax. Pressure on the cysts did not collapse them. The cysts varied in size from 1 mm. upwards, and the epithelium of the smaller cysts was cuboidal as in the alveoli, but larger cysts had ciliated columnar epithelium as in bronchi. Elastic fibres were not seen in the cyst walls, possibly because these develop at a later stage in pregnancy, and there were no inflammatory signs. Wolman considered that the cysts were due to an anomalous pinching-off of some developing bronchi and distension with secretion. He did not explain how the majority of the cysts came to be empty at necropsy; they must have contained gas or fluid at some time because of their round shape. Zipkin's case is particularly interesting because the bronchi of the large cystic left lung contained a layer of striated muscle; the right lung was aplastic and there were several congenital heart defects. The literature also includes numerous records of pulmonary cysts that have been found at necropsy in newborn infants less

ANALYSIS OF 374 CASES OF LUNG CYSTS IN CHILDREN (SCHENCK, 1937)

Type of Cyst		Distribution (%)	Age of Recognition in 368 Cases	Symptoms
Solitary	Multiple			
141	233	Right lung, 42	At birth, 36	Cough, 217
49 (fluid)	38 (fluid)	Left lung, 37	0-1 year, 57	Dyspnoea, 154
55 (air)	188 (air)	Bilateral, 21	1-15 years, 68	Expectoration, 152
37 (valvular expansile)	7 (valvular expansile)		Over 15 years, 207	Cyanosis, 75
				Fever, 72
				Haemoptysis, 52
				Malnutrition, 50
				Thoracic pain, 39

than 1 month old (Couvelaire, 1904; Stoerk, 1897; Pappenheimer, 1912; and Koontz, 1925). Pappenheimer's case lived three hours. At necropsy, the right upper lobe was full of cysts which could not be filled by bronchial injection, but he thought that microscopically there was continuity between the bronchi and the cysts. The obstruction was due to redundant bronchiolar epithelium. Koontz's case showed similar findings.

In summary, it can be stated that a congenital origin is generally assumed for most pulmonary cysts in childhood, because very similar cysts are found in the lungs of stillborn and newborn infants, aberrant lung tissue is usually cystic, and some few cases have shown associated malformations of other structures. The cysts are bronchial dilatations which may or may not be connected with the rest of the bronchial system, their lining is composed of respiratory epithelium, their walls are formed of bronchial structures which are frequently arranged in an irregular manner, and some appear to contain tumour-like masses. There is in the stillborn and newborn case little evidence of inflammatory pathology either in the form of infiltration with polymorph or lymphocyte cells, or of destruction in the cyst walls and replacement by fibrous tissue.

The following case is an example of a congenital cyst of lung.

The baby was born at 34 weeks' gestation, and weighed 3 lb. 4 oz. He succumbed after five minutes of life. The mother was a primipara aged 30. A year previously she had consulted her doctor because of sterility, and an undeveloped uterus was found. After dilatation and curettage and injections of gonadotrophic hormone she became pregnant. The pregnancy was normal, and no reason could be found for the premature rupture of membranes which precipitated labour.

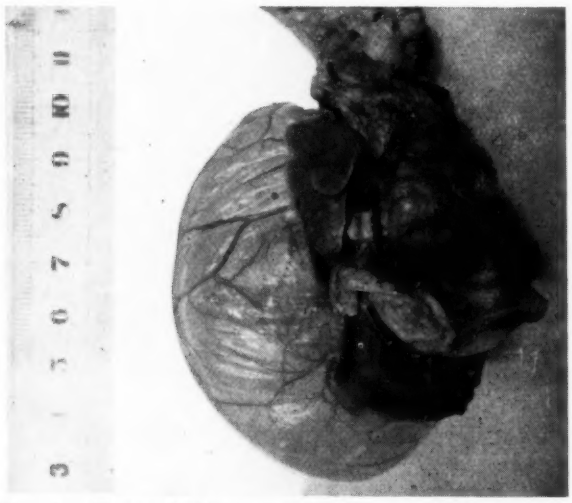

FIG. 1.—Congenital lung cyst found in a child who died five minutes after birth (Case 1).

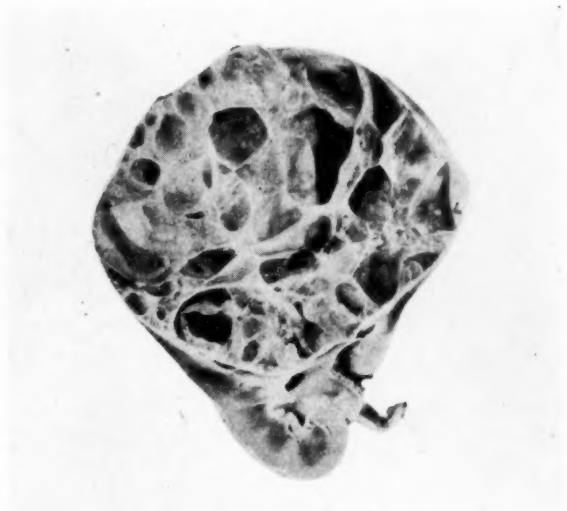

FIG. 2.—Cystic hygroma of right kidney (Case 2).

A necropsy was performed on the infant 24 hours after birth. There was a small subarachnoid haemorrhage over the brain. The abdomen contained a considerable amount of ascitic fluid, the cause of which was not found. The only other abnormal findings were in the thorax. The pleural cavities were clear. The right lung was bi-lobed; the third lobe appeared to be replaced by a cystic swelling occupying almost all the right pleural cavity and containing about 10 oz. of straw-coloured fluid (Fig. 1). Pressure on the cyst did not empty fluid into a bronchus. Traversing behind the cyst were the oesophagus, which was atretic here, and the aorta. Behind both of these an extension of the cyst crossed the midline. The right lung was markedly hypoplastic. The heart was normal.

The cyst was lined by low cuboidal epithelium and the section also showed a blood vessel and a nerve. The presence of cuboidal epithelium signifies that the cyst was pulmonary and not formed from pleural, vascular, lymphatic, or oesophageal tissue.

Case 2 shows a cyst which is probably of congenital origin.

Case 2. This girl was admitted to hospital when 1½ years old because of failure to thrive for six months, dyspnoea, and a swelling in the right flank for two weeks. The abdominal mass was found at operation to be a huge lymphangiomatous tumour of the right kidney, lined by flat endothelial cells (Fig. 2). It was noted at the time of admission that the trachea and mediastinum were deviated to the left and a radiograph showed that the right chest was filled by a huge air cyst (Fig. 3). The cyst had a bronchial connexion and appeared to be

enlarging, but after a needle was introduced to let off some air a tension pneumothorax developed, and the cyst deflated to a small area of lymphangiomatous material attached to the right lower lobe, diaphragm,

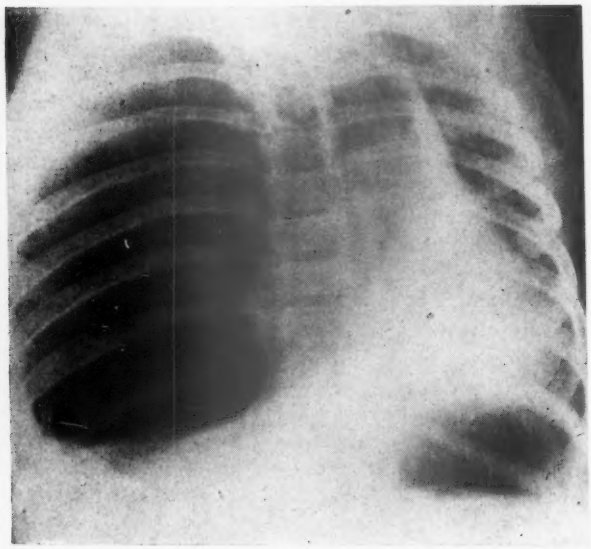

FIG. 3.—Large air cyst filling the whole right chest in a child of 1½ years (Case 2).

and parietal pleura. At operation, the three lobes of the right lung were tightly collapsed, and it was observed that the medial part of the cyst had previously herniated through the upper mediastinum and reached the lateral wall of the left upper chest. The cyst was removed, and the right lung subsequently inflated completely. Histological examination of a portion of the cyst wall revealed a lining of endothelial cells similar to that of the cystic hygroma of the right kidney. The lymphangiomatous tumour attached to the right lung could be taken as a congenital lesion, but its connexion with a bronchus and subsequent inflation might be due to an acquired valvular bronchial mechanism produced by pressure of the tumour.

Acquired Hypothesis

It is not possible to present the case for an acquired aetiology of pulmonary cysts with an equal wealth of supporting opinion from the literature concerned, but it should be mentioned that the evidence for a developmental aetiology, in many cases described as congenital, has been slender or even equivocal. The burden of this article is not to criticize the observations of others, nor to doubt that some lung cysts are indeed developmental, but rather to present clinical evidence to support the hypothesis that the majority of pulmonary cysts are acquired.

Acquired pulmonary cysts are generally the product of mechanical and inflammatory forces. The result of the latter hypothesis is best seen in the morbid specimen, while the former can only be estimated, though crudely, in life, and it is therefore obviously difficult to offer an adequate classification. There are bound to be gradations from cysts due to purely mechanical factors to those necrotic cavities which are entirely the result of infection. Misconceptions often result when disease processes are too rigidly classified, but as clarity demands some subdivision of the subject, the following has been used: (1) emphysematous and interstitial bullae, blebs and pneumatocoeles; (2) lung abscess, pulmonary infarction with necrosis, and bronchial distension; (3) tuberculous cavitation; (4) multiple honeycomb lung; and (5) traumatic cysts.

Emphysematous and Interstitial Bullae, Blebs, and Pneumatocoeles. Heller (1885) and Francke (1894) attributed so-called congenital cystic disease of lungs to the saccular dilatations of small bronchi and bronchioles formed in atelectatic lungs which did not expand after birth. Other writers ascribed honeycomb cysts with a cuboidal cell lining to the over-distension of the relatively few alveoli which develop in an atelectatic lobe. The following case illustrates the possible mechanism.

Case 3. This girl was noticed to be breathing poorly after birth. A chest radiograph taken four days later showed atelectasis of the whole right lung and a small pneumothorax on the left side. There was also a translucency on the right side in the region of the third to fifth thoracic vertebrae which had a sharp edge laterally. This was suggestive of partial aeration of the upper lobe or an air cyst, but it was in fact part of the over-inflated left upper lobe which had herniated across the mediastinum. Another radiograph 16 days later

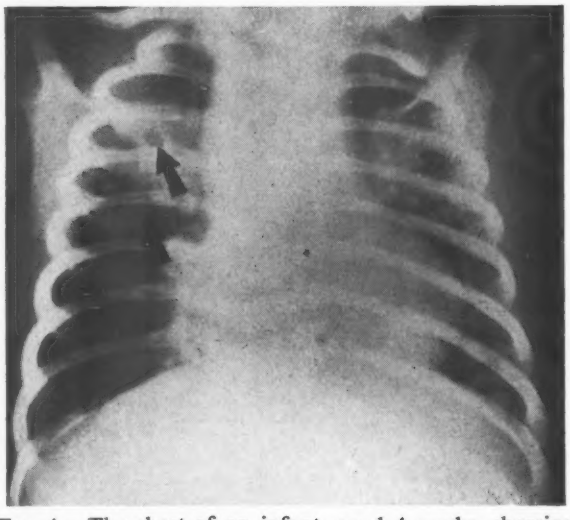

FIG. 4.—The chest of an infant, aged 4 weeks, showing two cystic areas, one in the atelectatic right upper lobe and the other in the middle lobe. There is also a pneumothorax on the left side (Case 3).

showed that the right lower and middle lobes had expanded, the pneumothorax cleared, and the heart was more central. There was also some expansion of the right upper lobe together with a translucent area resembling a cyst in its lower part. Further radiographs at 4 weeks old (Fig. 4) revealed two cystic spaces in the right upper lobe and a return of the pneumothorax on the left. The cysts disappeared during the next two months, but the lobe took three years to expand fully. At the end of this time a bronchogram showed bronchiectasis in the posterior bronchi (Fig. 5).

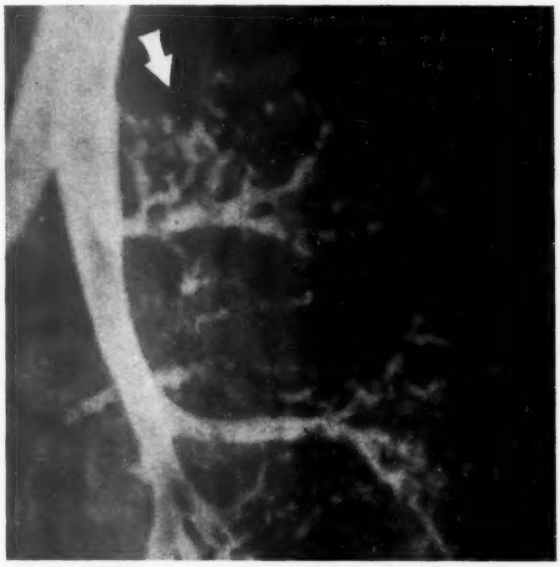

FIG. 5.—Oblique view of part of the right bronchogram done at the age of 3 years. There is bronchiectasis in the posterior segment springing from the eparterial bronchus just below the bifurcation of the trachea (Case 3).

The two translucent areas resembling cavities are either over-inflated lobules which contrast with the opacity of the atelectatic lobe, parenchymatous or interstitial bullae, or two bronchi distended into air cysts. The over-distension of alveoli may be either compensatory, or the result of valvular bronchial obstruction. The septa between emphysematous alveoli are liable to atrophy so that bullae are formed and if the bronchial obstruction remains, or infection thickens the cavity walls, these lung cysts are likely to persist. The residual bronchiectasis is in favour of the cysts being of bronchial origin, but it may be coincidental.

Case 4. This case demonstrates an almost similar radiographic appearance in a young baby, but with a different aetiology. This boy was the first live birth after six miscarriages. He was born a month prematurely, weighing 6 lb. 7 oz. and had blue asphyxia. When 2 weeks old, he developed a cough with expectoration of mucus but radiologically the chest was normal at the age of 3 weeks. Despite the cough, he appeared fairly well and when he was again examined at 5 weeks old he had gained a pound in weight: the temperature was 99° F.; pulse 150/min. and respirations 35/min. Bouts of coughing caused vomiting and dyspnoea. The chest revealed a slight wheeze in the right upper half and some bilateral basal crepitations. A radiograph showed complete opacity of the left upper lobe with a rounded lower border (Fig. 6). He was given a course of sulphamezathine. His general condition remained good, and the pulse and temperature were unaltered during the next week. His respirations, however, rose to 50/min., and he coughed up blood-stained mucopus (W.B.C. 24,400/c.mm.). A post-nasal swab grew pneumococci, *H. influenzae*, diphtheroids, and *Staph. albus*. At the age of 6 weeks one large and several small round clear areas appeared in the middle of the opacity in the left upper lobe (Fig. 7). Two months later the apparent cysts had cleared. The lobe was not fully expanded three years later when a bronchogram was done showing bronchiectasis in the apical and posterior segments (Fig. 8).

Without the earlier radiography showing a clear lung field on the left side, this child might have been considered as a case of infected atelectasis. In fact, he had pneumonia in the upper lobe, and as this was resolving, several collections of alveoli and small bronchi became over-distended owing to a check valve obstruction to their proximal bronchi. In the past many such cases have been diagnosed as fluid-containing congenital cysts of lung which ruptured into bronchi, the mucus then being coughed up and replaced by air. It is said that many such developmental cysts clear completely, but the advent of infection sometimes causes a valvular obstruction and distension of the cavities with air. In this child the emphysematous bullae and distended terminal tubes could have persisted as lung cysts had clearing of their bronchi not taken place and allowed them to deflate.

These transient cysts have been called ' pneumatocoeles ' to distinguish them on the one hand from permanent atrophic emphysematous bullae such as are found in adults with chronic bronchitis, asthma, or in lung fields scarred by old tuberculosis; and on the other hand from the pulmonary cavity of a lung abscess, localized infarction with necrosis of the parenchyma, tuberculous excavation or traumatic lung cyst. The conception of a pneumatocoele is recent, but there are now many descriptions of them (Peirce and Dirkse, 1937; Benjamin and Childe, 1939; Caffey, 1940; Almklov and Hatoff, 1946).

Pneumatocoeles are cavities on the surface or in the substance of the lung. They generally occur in children during the course of pneumonia and are sometimes multiple. Many contain fluid, their size and number may vary from time to time, and they show a marked tendency to complete resolution within a matter of days or weeks. The fact that pneumatocoeles tend to appear a few days after the start of pneumonia and contain inflammatory exudate, causes them to resemble a lung abscess very

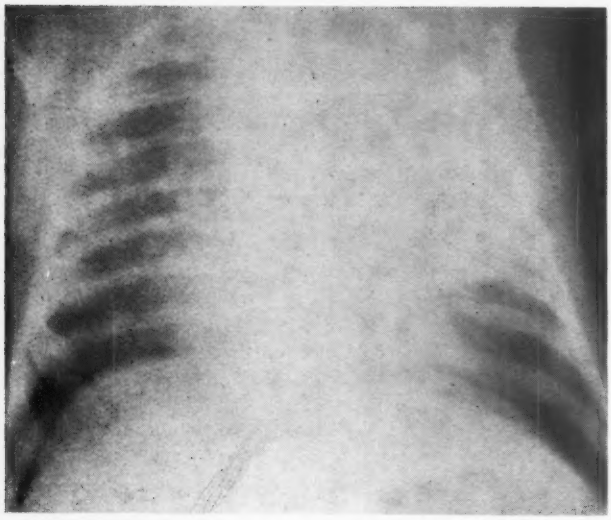

FIG. 6.—Pneumonia left upper lobe; age 5 weeks (Case 4).

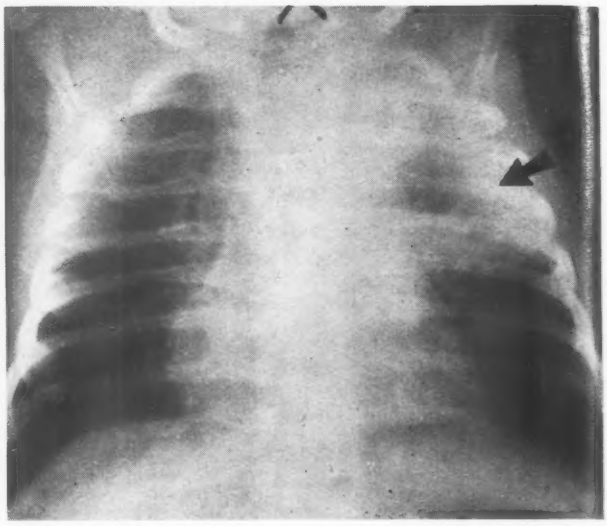

FIG. 7.—Air-containing cystic spaces in the clearing pneumonic lobe; age 6 weeks (Case 4).

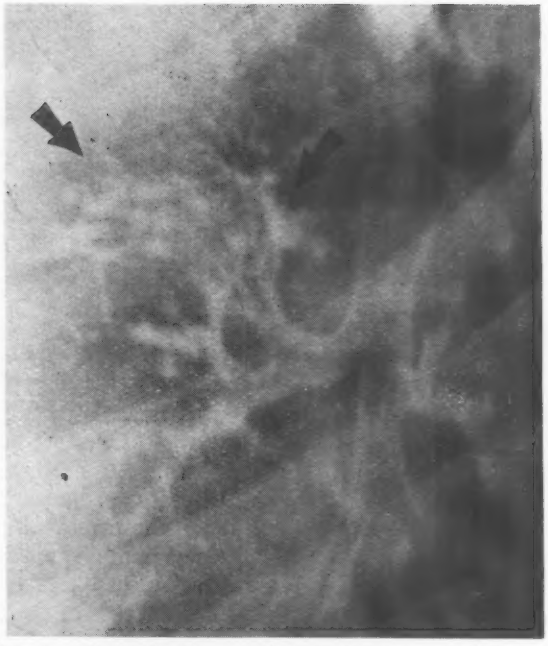

FIG. 8.—Part of oblique left bronchogram at the age of 3 years. Bronchiectasis in the left apical and posterior bronchi (Case 4).

closely, but their rapid development, fluctuating size and tendency to early and complete resolution are distinctive; furthermore the patient's clinical condition is seldom affected by their appearance and the prognosis of the illness is not made worse.

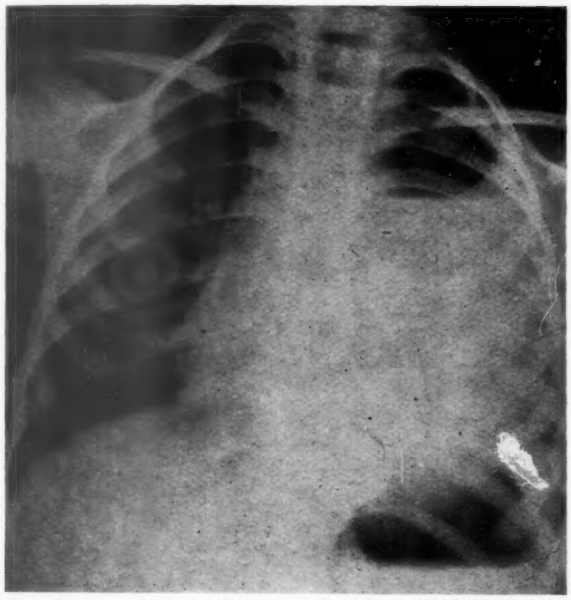

FIG. 9.—Pneumatocoele containing air and fluid in a child on the fifth day of pneumonia involving the left lung (Case 5).

It is thought that pneumatocoeles are produced by a valvular obstruction in small bronchi or bronchioles which causes the peripheral air pressure to rise and distend the local alveoli, bronchioles, or terminal bronchi into air-containing bullae. Such a mechanism seems probable, for air blebs and bullae are usual findings at necropsy on children with bronchopneumonia (McNeil, MacGregor, and Alexander, 1929); and obstructive emphysema of marked degree can sometimes be seen radiologically in infants with pneumonia (Snow and Cassasa, 1937). Laurell (1929) has demonstrated experimentally in fresh calf lung that raised intrabronchial pressure can produce emphysematous bullae both on the surface and deep in the substance of the lung which show up as round or oval cysts on radiography. Arnell (1927), and Doub (1928) have shown that the ring translucencies in the x-ray film of human lungs can be produced by emphysematous bullae surrounded by a rim of collapsed alveoli. The presence of a check valve bronchial mechanism has been confirmed by finding a raised gas pressure within pneumatocoeles (Lister. 1941; Caffey, 1940). A loculated pneumothorax can produce a round or oval air cyst radiographically as described by Fishberg (1917), but Peirce and Dirkse (1937) have shown by inducing a pneumothorax in one of their cases that the pneumatocoele was situated within the lung parenchyma.

It is quite possible that many pneumatocoeles are not emphysematous alveoli, but are in fact subpleural air blebs or interstitial pockets of air due to perforation of a small bronchus by ulceration or rupture of some alveoli allowing air into the tissue planes. The frequent occurrence of interstitial emphysema is proved by necropsy examination and histology in bronchopneumonia (McNeil, MacGregor, and Alexander, 1929). My earlier cases illustrate that when there has been bronchial obstruction and infection bronchiectasis can remain even when the cysts resolve satisfactorily. It is clear that a similar process may well result in diffuse cystic dilatations in the affected part. Pneumatocoeles may be of considerable size. When buried in the parenchyma of the lung they are round, but when more peripherally placed they can be elongated and resemble a pyopneumothorax as in the next case.

Case 5. A girl, 3½ years old, was admitted to hospital because of a cough, tachypnoea, fever and malaise for five days. She was given a course of sulphathiazole, but her temperature remained elevated for ten days. On examination, there were signs of pneumonia over the whole left lung and this was confirmed radiologically. Three days later her postero-anterior chest radiograph suggested a pyopneumothorax (Fig. 9), but a lateral view demonstrated a large, sausage-shaped pneumatocoele containing air and fluid. Another radiograph taken on the tenth day of her disease revealed two large cysts (Fig. 10). At no time did she expectorate any sputum

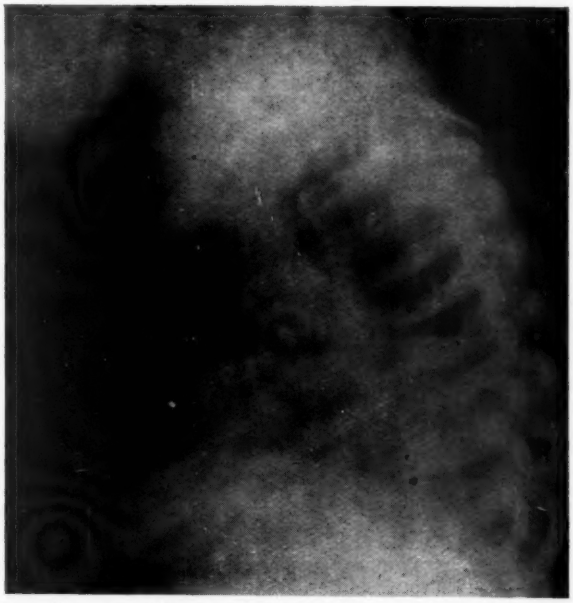

FIG. 10.—Two large pneumatocoeles on the tenth day of the pneumonia (Case 5).

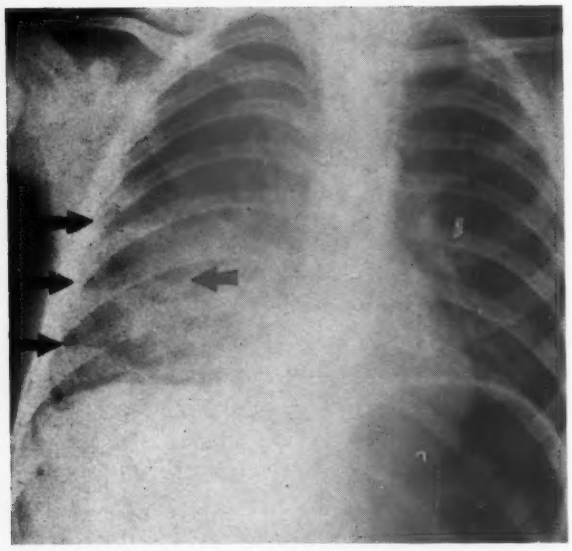

FIG. 11.—Four cysts in the right lower lobe with surrounding consolidation (Case 6).

FIG. 12.—Six weeks later and following an acute pneumonic episode. Giant cyst formed by coalescence of the four previous cysts or the gross expansion of one of them due to a valvular bronchial obstruction (Case 6).

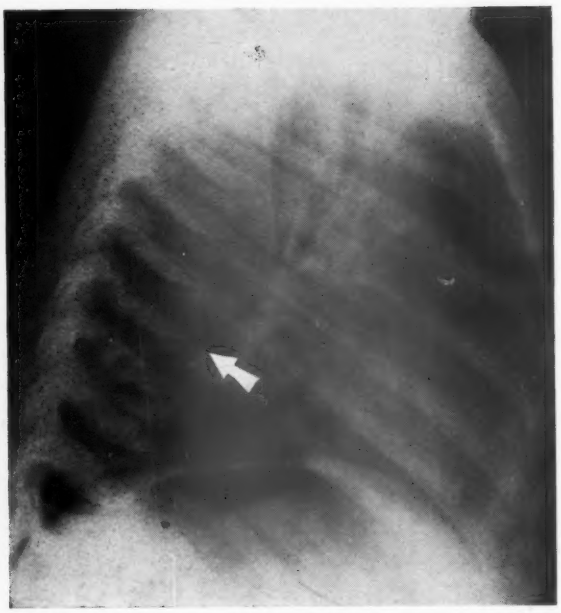

FIG. 13.—11 months later. Cyst now small and thin-walled in apical segment of right lower lobe (Case 6).

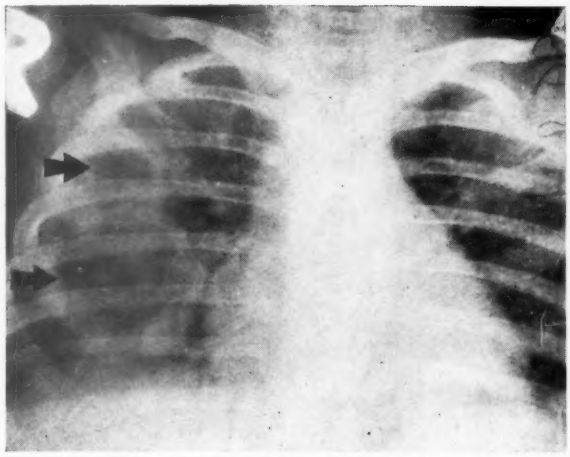

FIG. 14.—Two thick-walled cysts in the right lung surrounded by bronchopneumonic opacities (Case 7).

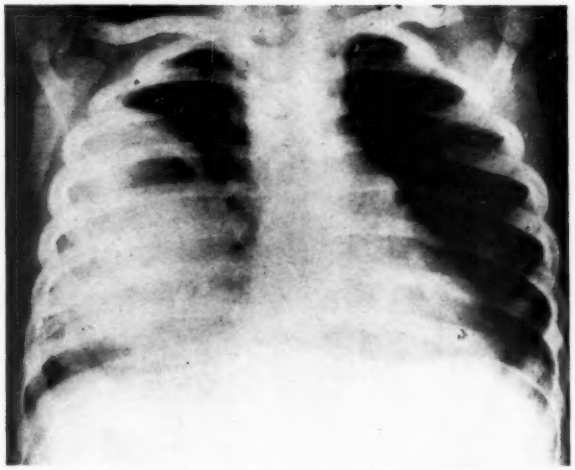

FIG. 15.—After three weeks of fever the radiograph shows one large cyst partly filled with fluid and surrounded by pneumonic consolidation (Case 7).

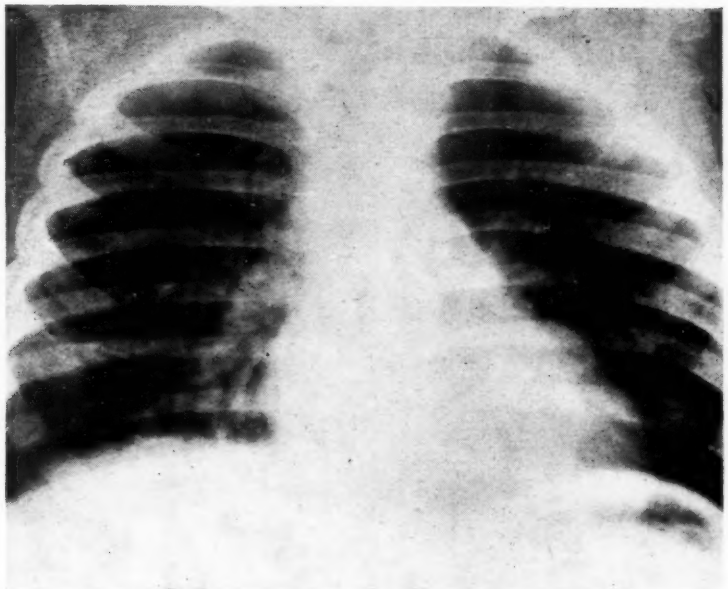

FIG. 16.—Four months after admission only faint circular outlines remain in the right lower zone signifying residual fibrosis (Case 7).

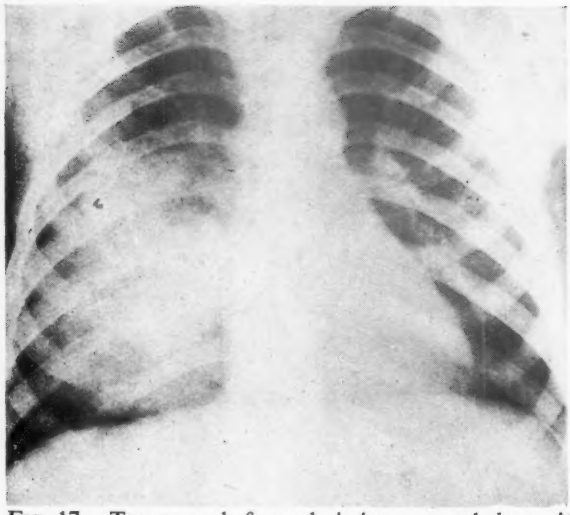

FIG. 17.—Two years before admission a rounded opacity in the centre of the right lung with a fluid level in the upper part caused by a large cyst filled with infected fluid and surrounded by consolidated and collapsed lung. This inflammation cleared in three months leaving one thin-walled air cyst (Case 8).

FIG. 18.—On admission pulmonary infection superimposed on the previous cyst has produced many more cysts containing infected fluid (Case 8).

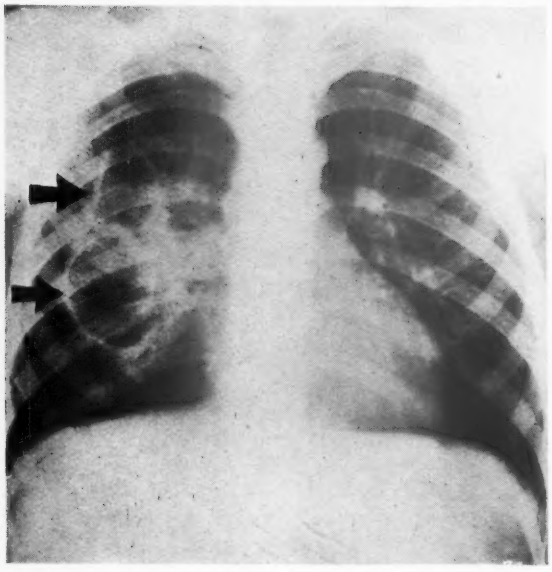

FIG. 19.—One month later two large air cysts remain (Case 8).

and her chest film was normal six weeks after the beginning of her illness.

Lung cysts starting as pneumatocoeles or lung abscesses may persist if the bronchial obstruction remains. Recurrent bouts of pneumonia are then not unusual and the thickened walls of the cavities decrease the chance of the cysts resolving completely. If the bronchial obstruction becomes a check valve the cysts may enlarge to an enormous size as in the next case.

Case 6. This girl of 2½ years had measles and pertussis four months before admission. She appeared to recover well from these, but five weeks before coming into hospital her cough returned and was accompanied by malaise. On admission she had the dense opacity of a pneumonia of the right middle and lower lobes. An earlier radiograph taken two and a half weeks before admission showed four cysts containing fluid and air in this area, surrounded by some pneumonic consolidation (Fig. 11). These cysts had probably developed during her earlier illness, and she now had an exacerbation of the inflammatory process. She ran a high fever for the next few weeks, there was no expectoration of sputum, and as the pneumonic process resolved the cysts again became apparent. A check valve obstruction to their bronchi, however, caused them to expand enormously and to coalesce into one enormous air cyst with fluid in its lower part which filled the hemithorax (Fig. 12). The cyst slowly deflated until 11 months later it was quite small, thin-walled and situated in the apical segment of the right lower lobe (Fig. 13). Two and a half years later the cyst had completely cleared and all that remained was a little local fibrosis.

The duration of lung cysts in childhood is very variable. Many last only a few days or weeks. Others, such as in Case 7, appear thick-walled, yet a bout of infection produces complete resolution. Some few, as in Case 8, persist unchanged through several bouts of infection and show little inclination to clear.

Case 7. This girl, aged 1½ years, had started a cold ten days previously, and became worse five days later by developing acute otitis media and bronchopneumonia. Her first radiograph on the tenth day of the illness showed two cysts embedded in the right lung, with mottled bronchopneumonic shadows about them (Fig. 14). She ran a high fever for the next six weeks. After three weeks, her chest film demonstrated a huge, rounded opacity resembling a fluid-filled cyst with a bubble of air in its upper part (Fig. 15). Three months later the cysts could not be clearly seen radiologically though a few circular traceries indicated some residual fibrosis in the previously affected area (Fig. 16).

Case 8. This boy came to hospital when five years old. At the age of 3 he had pneumonia, and a radiograph two months later demonstrated a large opacity which was then taken to represent a loculated interlobar empyema, but which was in all probability a cyst filled with infected fluid and surrounded by inflammatory exudate (Fig. 17). Within three months the opacity had cleared but a thin-walled cyst was clearly visible. This persisted for two years, when infection recurred, and the patient was again admitted to hospital. A radiograph of the chest at this time showed two large fluid-containing cysts and many small ones (Fig. 18). Had this radiograph been taken in the supine position instead of the erect, the alteration in the level of the fluid could have concealed the presence of cysts. Within two months the infection had almost cleared, but the two cysts remained clearly outlined (Fig. 19). The cysts gradually decreased in size, but, as at the time it was considered that the patient might have recurrences of pneumonia, the affected lobe was removed surgically.

When a large cyst is found in a child who has a history of pulmonary infection, it is probable that the cyst was caused by bronchial inflammation and obstruction. Cases are, however, seen without any history of an acute fever or chest disease which may have initiated the cysts.

Case 9. This boy was seen when 7 months old because of tachypnoea which had continued for three months. He had a normal birth. There was no asphyxia and no previous illness or chest symptoms. A radiograph of the chest (Fig. 20) revealed a large cyst filling the left chest, herniating across the upper mediastinum and compressing most of the lung parenchyma towards the heart and diaphragm.

A cyst such as the one described above is generally regarded as congenital in origin, because it has a

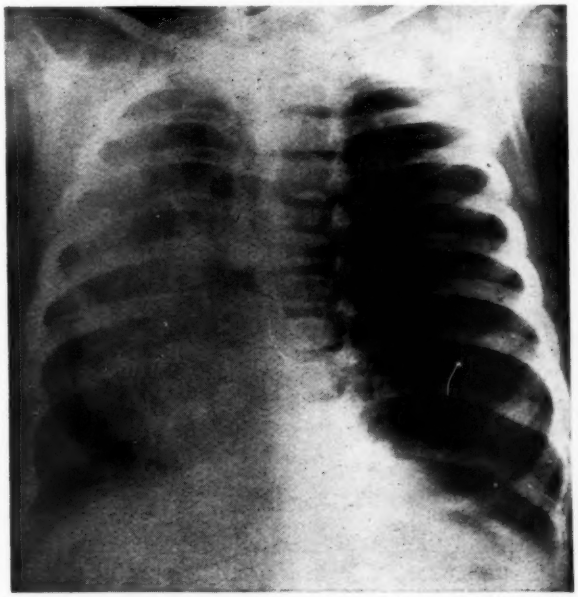

FIG. 20.—Aged 7 months. Large air cyst filling the whole of the left chest, displacing the mediastinum, and in the upper part herniating through the mediastinum into the right chest (Case 9).

uniform lining of cuboidal epithelium, there is seldom a history of an acute pulmonary infection, and the cyst persists relatively unchanged for months or years. It could have started like my first case, which showed a true congenital cyst full of fluid, and in which, after rupture into a patent bronchus, the fluid was coughed up and replaced by air. I do not think many large air cysts occur in this way, for at operation a developmental deficiency or agenesis of parenchyma is not found, but the cyst appears rather to spring from within a lobe and to compress the rest of its parenchyma together with the other lobes about its periphery. According to one argument in favour of a congenital origin, it has been claimed that bronchi enter tangentially rather than directly into such a cyst, and that surrounding bronchi rarely show chronic inflammatory changes, whereas in saccular bronchiectasis the bronchi are almost invariably the seat of chronic inflammation and enter the sacs directly. Cysts and bronchiectasis of infective origin can, however, both develop without severe necrosis of lung tissue so that the walls have fairly normal bronchial layers and an epithelium rendered cuboidal by gross distension. Some cases of large solitary lung cyst show at operation or necropsy that the large cyst is surrounded by many smaller ones, but that the whole is confined to a single segment or subsegment of lung. Histology reveals that in these cavities there is often a good epithelium and elastica but little muscle and no seromucus glands or cartilage; furthermore the quantity of alveolar parenchyma in the part is deficient.

The protagonists of a congenital aetiology point out that muscle and cartilage would not disappear by atrophy or inflammation without leaving some tell-tale fibrosis. In favour of an acquired aetiology, on the other hand, it can be said that as alveolar elastica is poorly developed and stains faintly at birth (Linser, 1900; Dubreuil, Lacoste, and Raymond, 1936), and as bronchial elastica is not only less abundant at birth than it is afterwards, but appears later in foetal development than muscle or cartilage, it is unlikely that a congenital failure to form would affect the latter while the embryologically later elastica flourishes.

A large solitary air cyst filling the hemithorax has been considered to have a different origin from polycystic lung disease, because it is seen much more often among infants than in older children and adults, and not infrequently causes serious respiratory embarrassment. The macroscopic specimen, however, usually shows other cysts in the same lung area which were too small to be visualized radiologically, and in many cases were collapsed into elongated, tortuous channels by the gross enlargement of one particular cyst. It is possible that the large tension cavity in this boy originated from a valvular obstruction by developmentally redundant epithelium, but as similar cysts are found in older children it is probable that the check valve resulted from a patch of local bronchial inflammatory swelling or mucosal hypertrophy associated with allergy or irritation. Once a balloon cyst of air has developed containing a high air pressure it can to a large extent be self-perpetuating. The bronchus to the cyst comes to be situated tangentially to its circumference. It dilates and the ostium opens with each inspiration, but bronchial narrowing during the less forceful expiration combined with compression of the slit-like ostium between bronchus and cyst impedes the expulsion of air. The cyst usually increases in size until an equilibrium is reached or further expansion is restrained by the chest wall and maximum capacity of the mediastinum to withstand displacement.

Lung Abscess, Pulmonary Infarction with Necrosis, and Bronchial Distension

The picture in some of the cases of pneumonic consolidation just mentioned, followed by the development of cavities containing air and fluid, suggests that the underlying pathology may be that of a lung abscess. A pneumatocoele is regarded as a gross distension of alveoli, small bronchi, or bronchioles without much destruction of lung parenchyma, whereas in a lung abscess there is a massive necrosis of lung tissue with the appearance of a cavity, as the dead material is removed by phagocytosis and bronchial drainage. Bronchial obstruction usually precedes the formation of a lung abscess, which is produced by localizing and enhancing the virulence of the accompanying infection. A lung abscess may therefore be a sequel to the aspiration of infected material after tonsillectomy or inhalation of a vegetable foreign body. Such episodes are, however, uncommon and the initial obstruction is generally due to swelling of the bronchial mucosa, or to viscid mucopus produced by bronchial inflammation or aspirated from the upper respiratory tract. Infected secretions retained beyond a block distend and then erode the bronchial walls and result in bronchiectasis. More virulent infection causes destruction of lung parenchyma as well, and produces the round cavity of a lung abscess. If the bronchial obstruction later becomes a valvular stenosis, air retained in the cavity can cause it to swell to a large size. An abscess cavity with a patent bronchial connexion has a natural tendency to decrease in size, but the raised intrabronchial pressure during the expiratory phase of

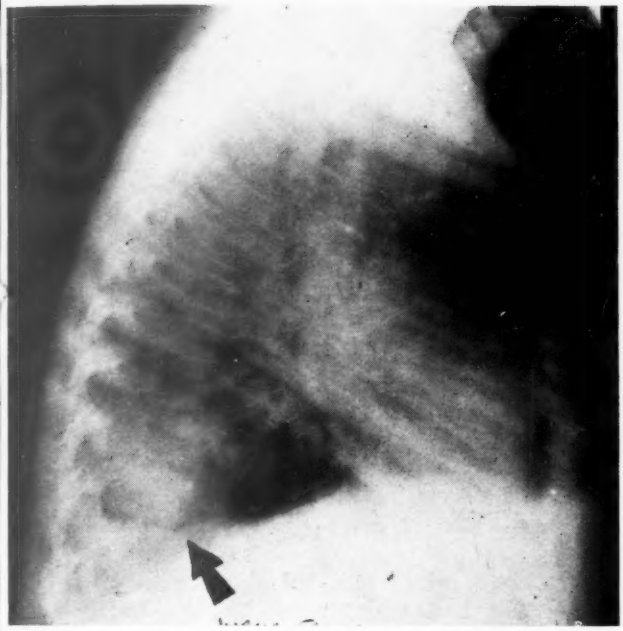

FIG. 21.—Segmental pneumonia in the right lower lobe on admission (Case 10).

FIG. 22.—Two weeks later most of the consolidation has cleared but an abscess cavity remains (Case 10).

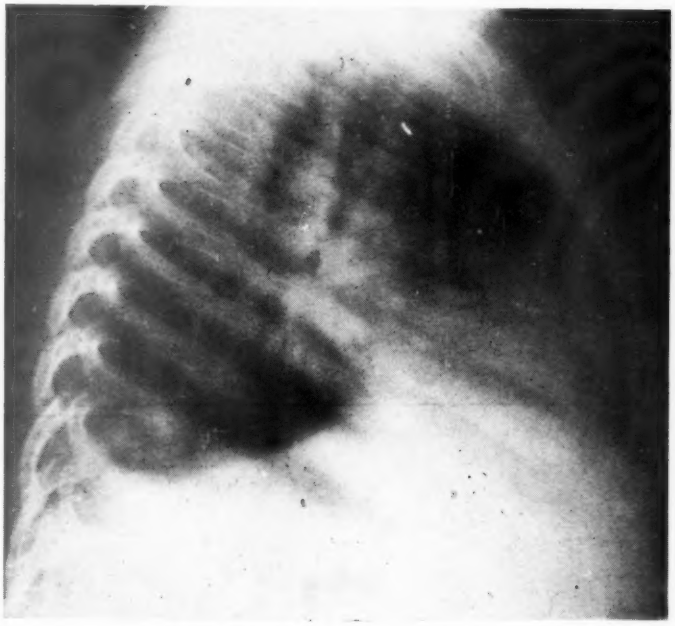

FIG. 23.—Seventh week. The abscess cavity has cleared (Case 10).

coughing may produce some distension. The finding of bronchial epithelium in the lining of cysts is no argument against such an inflammatory origin, for it is well known that this epithelium tends to proliferate and grow over raw areas in much the same way that skin spreads over denuded areas on the surface of the body (Robb-Smith, 1936; Pryce, 1948). Regenerated bronchial epithelium may be poorly ciliated and columnar in type, but often squamous metaplasia occurs or the stretching of the cavity wall results in an unciliated cubical mucosa. This altered epithelium lacks that rhythmical sweeping motion of cilia which carries mucus up the normal bronchial tree, and as a result secretions tend to be retained in abscess cavities or bronchiectatic sacs and predispose to further attacks of pneumonia.

Case 10. This case illustrates a lung abscess. A girl of 2½ years old suffered from chronic asthma, and was admitted during a severe attack accompanied by fever. Examination revealed signs of pneumonia at the right lung base (Fig. 21). She was given sulphonamides, penicillin, and antispasmodics, but remained febrile for one week and in status asthmaticus for three weeks. A radiograph after two weeks showed a thick-walled abscess cavity (Fig. 22) which cleared completely by the seventh week (Fig. 23).

A lung abscess in childhood may be secondary either to the aspiration of infected material or to the metastatic spread of infection from a septic focus elsewhere. Occasionally it occurs in the course of pneumonia, and in this case the responsible organism is the staphylococcus more often than the streptococcus, pneumococcus, or Friedländer's bacillus. All these organisms tend to cause a non-putrid lung abscess, and foul sputum mainly characterizes the lung abscess resulting from or complicated by anaerobic spirochaetes and fusiform bacilli.

Staphylococcal pulmonary infection accounts for less than 5% of pneumonias at all ages, but is relatively more common in early childhood, and in the pre-penicillin era it was accompanied by a considerable mortality (Heffron, 1939; Bullowa, 1937). It has been recognized that in addition to the fulminating type of staphylococcal pneumonia there is a relatively benign variety with a low fatality rate (Mac Keith, 1941 and Brock, 1945) have recently drawn attention again to the extraordinary frequency with which this type of pneumonia is accompanied by pulmonary cavitation. Staphylococcal pneumonia rarely occurs without some preceding illness, such as a cold or an attack of influenza. When developed, it is usually broncho-pneumonic in type, and is accompanied by prostration, fever, and slight cyanosis. Blood culture may yield a growth of *Staphylococcus aureus*, and it is common to find the organism predominating in the sputum. The infection is overcome more slowly than other pneumonias, and abscess cavities often appear in the denser areas of consolidation. These cavities are at first thick-walled and contain purulent exudate but in a short time some become thin-walled ' soap bubble ' cysts. The large cavities in staphylococcal pneumonia are reminiscent of pneumatocoeles, but the latter, unlike the former, are seldom accompanied by any recurrence of fever, increase in expectoration of sputum, deterioration in clinical condition, or raised mortality rate. Where the bacteriology was recorded in cases of pneumatocoeles recorded in the literature, the principal organism was usually either the staphylococcus, the pneumococcus, or the streptococcus. The pathology underlying a staphylococcal lung abscess and a pneumatocoele must be very similar, for in each the first appearance is often of a large fluid-filled cavity; later a segment of air is seen in it with a fluid level, and this in turn is succeeded by a thin-walled air cyst which eventually clears with little subsequent fibrosis. Brock (1945) has performed bronchograms on cases recovering from staphylococcal pneumonia and has shown that the bronchial tree is quite normal in some, while others have moderate but seldom severe bronchiectasis. Similar findings have been noted in some of my cases with pneumatocoele.

The pathological distinction between an abscess and a pneumatocoele is that the essence of the former is necrosis of lung tissue, whereas the latter is a cavity formed by the accumulation of air or exudate in a local area without much parenchymatous destruction. It does not seem to me feasible that the huge fluid-containing cavity of a staphylococcal abscess can be due to necrosis of tissue in any way commensurate with its radiological size, because resolution is so rapid and complete with little apparent residual fibrosis. It would appear that a staphylococcal lung abscess occupies an intermediate position between the air cyst that forms in the afebrile resolution phase of a pneumonia and the chronic cavity which results from the necrotizing process of an abscess due to anaerobic organisms. In clinical practice it may not be easy to establish a difference between an abscess and a pneumatocoele, but the point at issue here is that both are acquired lung cysts.

In adults there is a condition known as chronic or non-specific suppurative pneumonia (Logan and Nicholson, 1949) in which irregular consolidation occurs with a tendency to spread and form abscess cavities. No particular organism has been incriminated though many common ones occur in

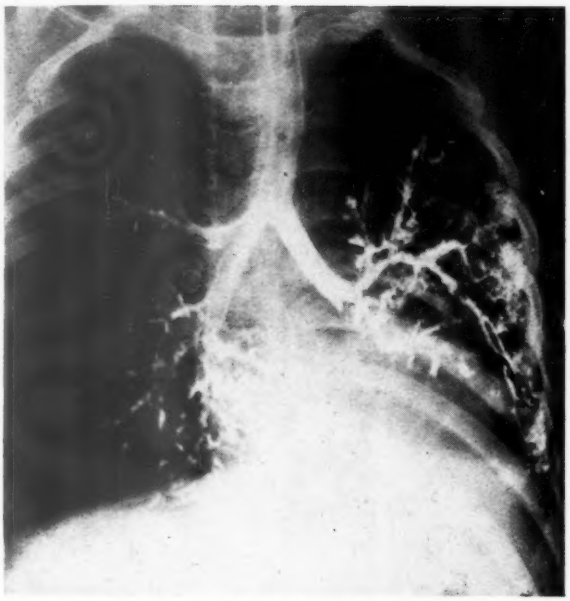

FIG. 24.—Well expanded left upper lobe one and a quarter years after a lower lobectomy and lingulectomy for bronchiectasis (Case 11).

FIG. 25.—Two years later the left upper lobe is small and fibrotic containing shrunken dilated bronchi (Case 11).

FIG. 26.—Saccular bronchiectasis following primary tuberculous infection one and a half years earlier (Case 12).

FIG. 27.—Cystic bronchiectasis in the right middle lobe two and a half years after pneumonia (Case 13).

the sputum. The patient is febrile from time to time for many weeks, and the eventual prognosis is not good. It is possible that a similar condition occurs in children and produces lung cysts.

A cavity in the lung may arise not only from inflammatory necrosis of parenchyma but also by a process of infarction. Kessel (1930) has described several patients suffering from pneumonia who developed thrombosis of pulmonary and bronchial arteries together with necrosis and excavation of lung tissue. It is only possible to prove the occurrence of such a mechanism in the morbid specimen, but it might be suspected when pulmonary cavitation appears without fever in the resolution phase of pneumonia.

The conception that lung cysts can form by gross distension of small bronchial tubes by inflammatory exudate, and that it is unnecessary to invoke the pathology of a centrifugal necrosis of lung parenchyma which characterizes a lung abscess, is well illustrated by examining a series of cases beginning with mild bronchiectasis and working up to those with severe bronchial dilatation.

Case 11. This child had a left lobectomy and segmental resection for bronchiectasis when 5½ years old, but the remainder of the left upper lobe did not expand for four weeks after operation. Fig. 24 taken one and a quarter years later shows that some bronchiectasis had developed in a dependent bronchus, and Fig. 25, two years later, demonstrates a small fibrotic upper lobe with dilated bronchi.

Case 12. The child was 4½ years old and had chest symptoms since Mantoux conversion one and a half years previously. His radiograph showed saccular bronchiectasis in the apical and posterior segments of the right upper lobe (Fig. 26). During his primary infection glandular enlargement or endobronchial tuberculosis had probably obstructed the main bronchi to these segments.

Case 13. This patient had pneumonia when 2½ years old, and since then a productive cough. Fig. 27 demonstrates extensive cystic dilatation in the bronchi of the right middle lobe.

The connexion between bronchi and large air cysts is illustrated by the following case,

Case 14. This boy, aged 2 years, attended hospital with a cough and fever. A radiograph of his chest two months earlier was quite normal, but on admission he had at least four air cysts; two at the right base, which were partially filled with fluid, and two at the left base containing air only (Fig. 28). Bronchograms done four months later demonstrated that these cysts could be readily outlined (Figs. 29 and 30) and that many smaller cysts existed. Five months after admission there was little evidence of these cysts on a plain x-ray film. Four years later the bronchograms were repeated, and all that remained was varicose and saccular bronchiectasis in place of the former cysts (Figs. 31 and 32).

The radiographs of this child show a most instructive sequence of events. The initial radiograph of the chest was normal, but later valvular expansile cysts at both bases with inflammation and consolidation at the right base appeared. The cysts suggested temporary pneumatocoeles formed by emphysematous bullae or distended bronchioles. Viscous oil used for bronchography seldom enters such large cysts, because exudate or pressure occludes the bronchi leading to them. However, bronchograms done on this boy four months later showed numerous cysts affecting some of the secondary and tertiary axillary and basal bronchi of the lobes involved. The bronchograms four years later demonstrated one large sacculation of the axillary branch of the right posterior basal bronchus and varicose bronchiectasis in some other axillary and dependent branches in both lower lobes. The left lateral bronchogram revealed a very important finding, namely that the bronchial varicosity, which was all that remained of the former cysts, affected the centre segment of only the tertiary bronchi, the terminal parts being normal in calibre. The cysts had therefore not been emphysematous bullae formed from alveoli, nor yet from bronchioles, but were on the contrary gross dilatations of small bronchi.

The cysts in this boy were not due to congenital malformation, for they were not present in his initial radiograph, and there is no justification for the assumption that empty developmental cavities were lying dormant until exposed by the air pressure

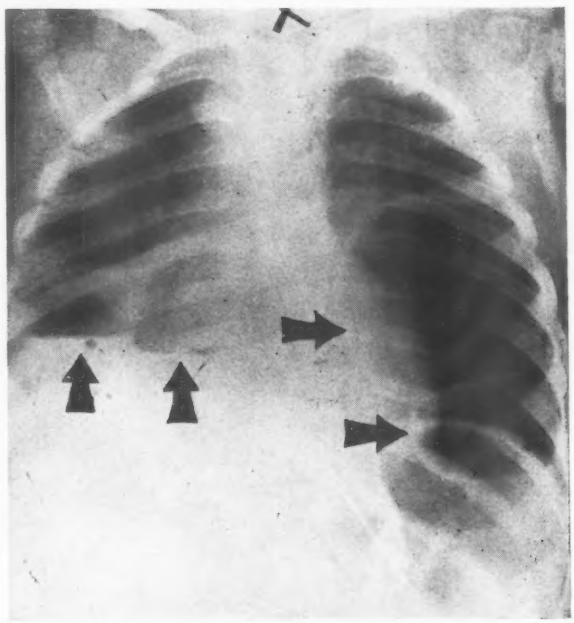

FIG. 28.—Boy aged 2 years. Two cysts at each base on admission (Case 14).

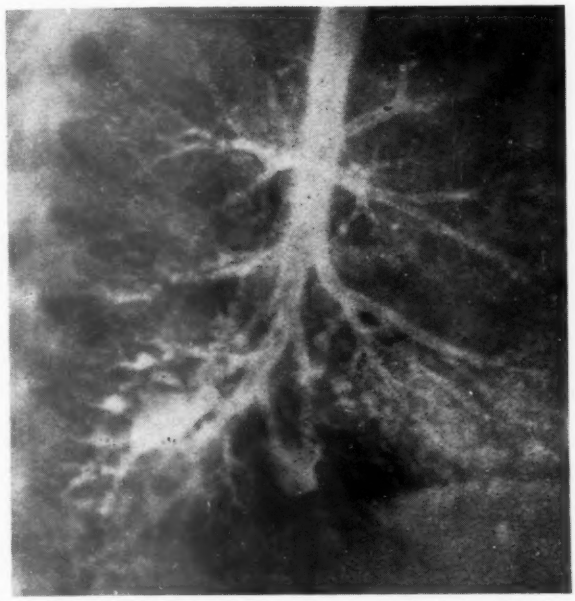

FIG. 29.—Right bronchogram four months later showing numerous cysts in the right lower lobe and two on axillary branches of a middle lobe bronchus (Case 14).

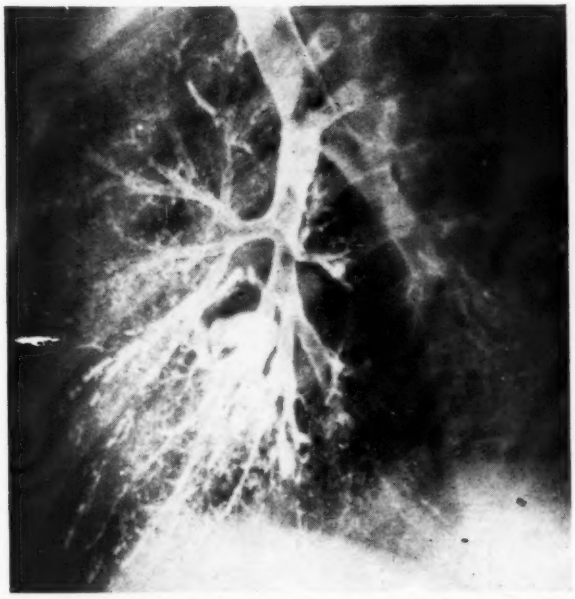

FIG. 30.—Left bronchogram four months later showing one large and several smaller cysts attached to the lower lobe bronchi (Case 14).

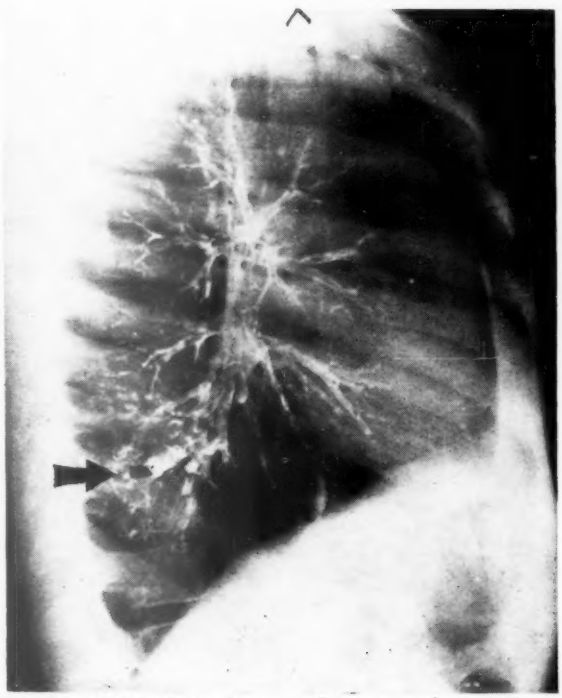

FIG. 31.—Right bronchogram four years later. Severe varicose and saccular bronchiectasis in the axillary branches of the lateral and posterior basal bronchi, possibly also of the cardiac bronchus (Case 14).

FIG. 32.—Left bronchogram four years later, showing marked varicosity of the axillary branch of the anterior basal bronchus and the same deformity of one of the smaller dependent branches of the middle and posterior basal bronchi (Case 14).

changes or hydraulic effects consequent on bronchial inflammation. The mere fact that the cysts subsided into varicose bronchial dilatations suggests that they were produced through distension of bronchi by air or exudate under pressure. Sacculations of acquired bronchiectasis, due to an obstruction in a major bronchus, affect the weaker peripheral portions of the bronchial tree, such as the tertiary divisions, more often than the firmer walled primary or secondary branches. The fine terminal bronchi and bronchioles are seldom dilated because they are effectively plugged by thick exudate. Eloesser (1932) has shown that a valvular obstruction of a main bronchus which causes a high peripheral air pressure produces collapse of the parenchyma after an initial temporary phase of hyper-inflation, and that the weak peripheral bronchi then become dilated, even when there is no concomitant infection. This boy must have developed an infection and then valvular obstructions in some tertiary bronchi which caused segments of them to dilate enormously. When the stenoses cleared they deflated, but so far have not assumed a normal calibre.

In the past, it has been almost a tradition to believe that round cysts are congenital in origin, and bronchiectasis on the other hand is an acquired disease. The futility of such a generalization is well exemplified by the next case in which there were round cysts and a congenital anomaly.

FIG. 33.—Aged 1½ years. Widespread varicose and saccular bronchiectasis in both lungs together with some round cysts, one of which springs from the right main bronchus in an abnormal position above the eparterial bronchus (Case 15).

Case 15. This girl of 1½ years had a productive cough since bronchitis at the age of 6 months. There was no history of pneumonia or of cyanotic attacks after birth. A bronchogram demonstrated varicose and saccular bronchiectasis in both lungs together with some round cysts, one of which sprang from the right main bronchi above the eparterial bronchus (Fig. 33).

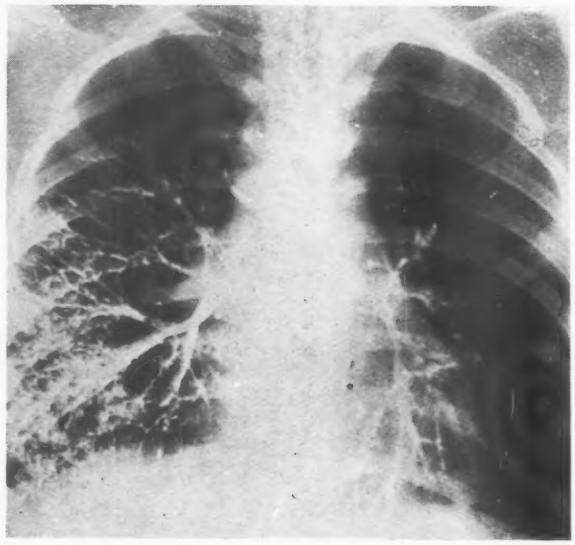

FIG. 34.—Bronchogram illustrating an anomalous bronchus of normal calibre arising from the trachea at the level of the carina.

The early age at which symptoms began, together with the widespread nature of her disease and the presence of a congenital anomaly, in this case suggested a developmental origin of the bronchial dilatations. A staphylococcal bronchopneumonia could have caused multiple cavities and bronchiectasis but this girl had no history of pneumonia. It is possible that multiple bronchial occlusions occurred in this child during or following the initial bronchitis, and the secretions retained caused the peripheral bronchi to dilate into bronchiectatic cavities or swell into cysts. It is not necessary to assume that she was born with a cyst attached to the right main bronchus, for this is as likely to have developed during an infection in an anomalous bronchus of normal calibre as shown in Fig. 34.

Polycystic disease of the lungs may be bilateral or entirely confined to one side. Most children with multiple cysts have had several attacks of pneumonia, and it is impossible to ascertain whether the cysts occurred during the course of one of them or originated earlier in a less severe pulmonary infection. A spread of bronchiectasis is rarely observed in children followed up for many years, despite their chronic bronchitis, yet in the cases of lung cysts described earlier, the number of cavities that can be seen varies from time to time,

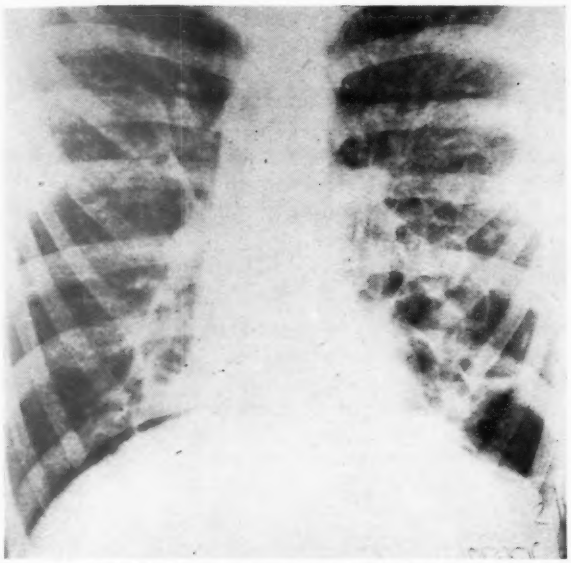

FIG. 35.—Multiple round cysts at both bases (Case 16).

FIG. 37.—The whole left lung in this boy is riddled with cysts of all sizes. Right lung quite normal (Case 17).

FIG. 36.—Operation specimen of the left lower lobe demonstrating the large size of some of the cysts (Case 16).

FIG. 38.—Operation specimen of the left lung showing it to be filled with cysts formed by wide dilatations of the bronchial system and that there is little remaining parenchyma (Case 17).

particularly after pneumonia. In the histology of bronchiectasis, the dilatations generally show almost complete destruction of the bronchial wall, and regeneration of mucosa over replacement fibrous tissue. Though round cavities in the lung can result from abscess formation, cysts of the lung usually reveal less severe destruction of the tunica propria, and it is probable that they occur more often from distension of bronchi distal to an obstruction when this is unaccompanied by virulent infection in the retained secretions. Cases 16 and 17 are examples of polycystic lung disease, the former being bilateral, and the latter affecting the whole of the left lung, while the right lung was quite normal.

Tuberculous Cavitation

A cavity at the site of a primary focus from necrosis of parenchyma is a very rare phenomenon. Third stage tuberculosis or phthisis occurring before puberty is also rare, but it must be considered when a lung cavity is observed in a child with a positive Mantoux reaction.

Case 18. This case illustrates a phthisical cavity in a boy of 7 years. This boy complained of bronchitis for two months together with listlessness and nocturnal sweats. His only previous illness was measles at the age of 4 years. The radiograph of the chest showed a calcified primary complex at the right apex and tuberculous infiltration and cavitation at the left apex (Fig. 39). Gastric lavage revealed numerous tubercle bacilli.

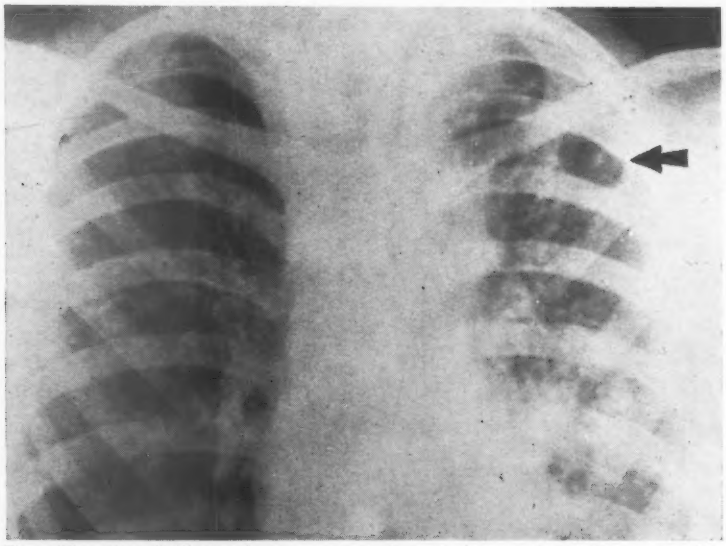

FIG. 39.—A calcified primary tuberculous lesion at the right apex with phthisical infiltration and cavitation at the left apex in a boy of 7 years (Case 18).

Case 16. This 11-year-old girl was admitted with a productive cough, gross clubbing of the fingers, and amyloid disease. At the ages of 2½, 8, and 9 years she had pneumonia but she complained of very few chest symptoms between these episodes. Her chest radiograph showed multiple cysts at the left base and a few at the right base (Fig. 35). The operation specimen of the left lower lobe demonstrates the size of some of the cysts (Fig. 36). A large bronchus can be seen to enter each of these cysts, and though they may be chronic smooth-walled abscess cavities, it is feasible for them to have developed by distension of the peripheral portions of the bronchi which connect with them.

Case 17. A boy of 3½ years had chest symptoms since pneumonia a year before. His chest radiograph showed that the whole left lung was cystic (Fig. 37). The whole right lung was normal as proved by bronchography. The operation specimen of the left lung is shown in Fig. 38, and it can be seen that the cysts are widely dilated bronchi.

Multiple Honeycomb Cysts

Oswald and Parkinson (1949) are of the opinion that an understanding of the genesis of cystic disease of lungs has been clouded by the tendency of most writers to group together all cases with cysts, instead of studying separately the different forms, such as the simple lung cyst, the multiple honeycomb lung, the cysts which appear to arise from bronchial tissue, and those which arise from alveolar tissue. They have studied the honeycomb lung with its collection of thin-walled cysts distributed uniformly throughout both lungs and varying in size up to a maximum of 1 cm. in diameter. They found that the clinical features of this group were distinctive: spontaneous pneumothorax which was often bilateral, and progressive

right heart failure which led to death. In their 16 cases, six formed part of a general medical disorder, namely xanthomatosis, biliary cirrhosis, tuberose sclerosis, and diabetes insipidus. Their remaining 10 cases were of uncertain aetiology, and they assumed that these widespread cysts arose as developmental abnormalities, or were secondary to mechanical factors from acquired disease. In favour of the former they quoted a case of Rubin's (1947) which, apart from multiple simple cysts, had a patent ductus arteriosus, congenital aneurysms of the pulmonary arteries, and anomalous coronary arteries. Arnheim (1898) described a girl of 1½ years with honeycomb cysts of lung who also had congenital hypertrophy of the right side of the body.

The histology of the honeycomb lungs reported by Oswald and Parkinson (1949) has been studied by Cunningham and Parkinson (1950). They recorded that the cysts generally involved bronchioles, and were widespread throughout both lungs. In some, the lining consisted of simple cuboidal epithelium, and in others histiocytes or just collagenous material. Giant cells were found both in the lining and in the interstitial tissue of most cases, and the stroma about the cysts was composed of granulomatous material with a good deal of interstitial fibrosis. Plain muscle and elastica were difficult to find in the supporting structures, probably because they had been destroyed by inflammation. The lung parenchyma was greatly diminished in quantity; in some few normal alveoli remained. This was probably due to atrophy rather than to a failure of development, for the majority of cases were adults and symptoms had only been present for a few years. A short history of illness, usually a few weeks or months, also characterized the cases reported in early childhood by Sharkey (1892-3), Tooth (1897), Fletcher (1901), Bernstein (1905), and Collins (1933). The last two authors recorded finding large giant cells in the cyst walls though there was no evidence of tuberculosis. In Bernstein's case there was cholangitis without cirrhosis of liver, and in Fletcher's there was cholangitis associated with fibrosis and marked dilatation of the bile ducts. Honeycomb lungs in childhood have also been found in association with xanthomatosis and biliary cirrhosis by Rowland (1928) and Farber, Hampton, and Mueller (1942). Most of these authors noted that the cysts could not be emptied into the bronchial system, but on microscopy they appeared to be formed from bronchioles, and the alveoli and main bronchi were normal.

The actual mechanism of production of these bronchiolar or bronchoalveolar cysts which make up a honeycomb lung is unknown. Some may be due to a widespread obstruction of small bronchial tubes by inflammatory swelling of the mucosa, but in most cases reported the cysts have contained clear, glairy fluid rather than thick pus. Infiltration about the cysts with reticulo-endothelial and giant cells has suggested a reticulosis or xanthomatosis in some cases, and it has been suggested that the condition may be a manifestation of pulmonary sarcoidosis. As the cysts are formed from bronchioles, but cannot be emptied into the larger bronchi, some infiltration of the walls or firm exudate must be the cause of the bronchial occlusion. Though in two children honeycomb lungs were associated with indisputable congenital lesions, the majority of reported cases at all ages were notably free from pulmonary symptoms and ill-health until a short time before death, and it must therefore be concluded that honeycomb cysts of lung are acquired rather than developmental in origin.

Traumatic Pulmonary Cysts

Following traumatic rupture of lung parenchyma or a bronchus a haematoma is formed, and as the blood absorbs or drains away through the bronchial system, air replaces it and forms a gas-filled cavity in the lung. Rupture of a bronchus rarely occurs without tearing the parenchyma, except near the hilum, but a bronchus occasionally develops a valvular air leak due to perforation by a patch of ulcerative bronchitis (Allison, 1947). The next child is a good example of a traumatic lung cyst.

Case 19. This boy, aged 6 years, was pinned to the ground by a large metal frame, weighing about 1 cwt., which fell on the right side of his chest. He was released in a few seconds, but coughed up blood for the next half hour. A radiograph of his chest made on the same

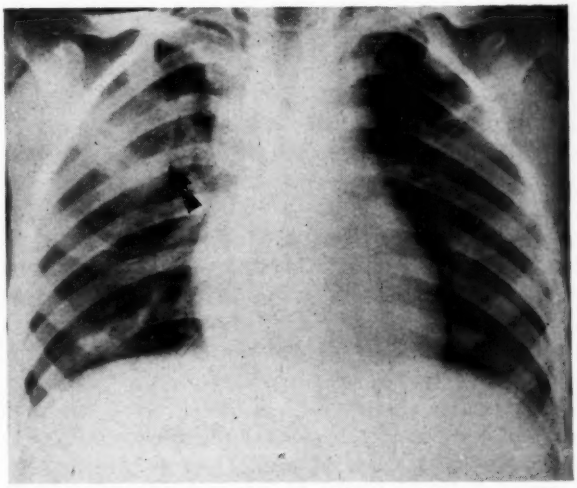

FIG. 40.—Traumatic air cyst of lung with surrounding haematoma three days after a blow over the right chest (Case 19).

day revealed a mottled opacity in the right upper lobe. By the next day a circular translucency was present in the opacity. The chest film taken on the third day after the accident is reproduced in Fig. 40, and shows clearly the air cyst surrounded by lung consolidated by extravasated blood. He remained afebrile throughout, and the haematoma cleared by the ninth day. Five weeks after the accident the cyst could still be clearly seen (Fig. 41) but it had disappeared by the ninth week.

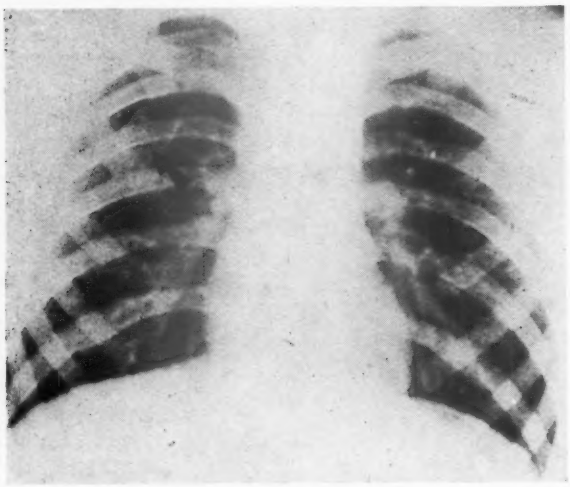

FIG. 41.—The air cyst in the right upper lobe is still present five weeks later (Case 19).

Discussion

Morbid anatomy attempts to deduce the processes of disease from a detailed study of many specimens at varying stages of evolution. Necropsy and operation material supply evidence of a static nature, and when cysts are found in the lungs the forces which produced them can only be surmised. An adequate knowledge of the vital changes in the body cannot be acquired from the limited field of cellular pathology, nor yet from bacteriology in which diseases are the predictable outcome of infection. An understanding of the dynamic processes which cause cysts to form in the lung can be gained more easily and accurately by clinical methods and the examination of serial chest radiographs of the same subject over a period of years. A list showing the age of the patients together with a careful description of the lung cyst in each would add little to present knowledge on the causation of cystic disease of the lungs, because the radiological appearances alter in response to changing mechanical forces and the powers of repair and destruction.

Congenital cystic disease of the lungs has a large literature, and many examples have been recorded in infancy. There can be no doubt that cysts in the lung are sometimes of developmental origin, but because such cysts can retain secretions and predispose to pulmonary infection, it is not necessary to assume that cavities in the lung after pneumonia have necessarily preceded it. A congenital aetiology is obvious when cysts are found in stillborn or newly delivered infants, but in any other age groups definite malformation must be observed which could not have arisen from an acquired pathology. After the first few days of life proof of a developmental origin can only be supplied from examination of the morbid specimen, and even this is unsatisfactory, for should a malformation not be found, it can be argued that all trace has been destroyed by postnatal infection. Collapsed or dormant cysts with evidence of congenital origin have rarely been observed in the lungs of children, but there is no doubt that cysts actually develop postnatally either because of infection or obstruction of bronchi. In this article cases have been cited to show the formation of cysts in lungs which, a short time before, were apparently quite normal. Such cysts not only appear, but enlarge, subside, or alter in number if observed over a long period of time, and these changes suggest that the cysts are the result of an acquired rather than a congenital mechanism.

Cavitation is usual in adult phthisis. Dormer, Friedlander, and Wiles (1945) have demonstrated by bronchography that there is always bronchial obstruction in such cases and very often bronchiectasis as well. The cavity formation is the result of tuberculous necrosis of the parenchyma but the bronchiectasis is due to bronchial obstruction and distension of the peripheral bronchi by inflammatory exudate. Emphysematous bullae are also frequent in a tuberculous lobe owing to a check valve mechanism in some of the finer bronchioles. Bronchography is rarely performed during an acute pyogenic inflammation of the lung, but there is reason to believe that the same events can occur though more rapidly. Inflammation of the bronchi produces swelling of the lining and exudation of mucus or mucopus. Occlusion of a bronchus predisposes to inflammatory destruction of its walls, and the retained infected secretions distend and dilate the peripheral tubes. Such dilatation may reach a marked degree in a week or two as has been demonstrated by the saccular cavities in experimental bronchiectasis, and those found in a person dying a few weeks after inhaling a foreign body. Occasionally the surrounding parenchyma becomes necrotic and a lung abscess results. A cavity in adult phthisis can distend into a balloon cyst because of a raised peripheral air pressure beyond a valvular bronchial obstruction, and as the same process may follow a pyogenic abscess in a child, it is plain that

some air-containing cysts are formed in this way.

In bronchiectasis, a disease generally considered to be acquired, the bronchial dilatations are usually all of the same type; cylindrical, fusiform, varicose, or saccular. It does not seem logical that round cysts should be assumed to be congenital when in fact their appearance suggests a more severe degree of bronchial dilatation than is common in bronchiectasis. Round cysts can occur in bronchiectasis which is undoubtedly acquired. It has been suggested that such cases can be distinguished from congenital cystic disease of lungs by the chronic inflammatory changes in the bronchi of the former which are absent in the latter. The argument does not bear critical examination, for even in acquired bronchiectasis there is disagreement among authorities on the amount of chronic inflammatory tissue and bronchial destruction which is to be found. Lander and Davidson (1938) consider it is very slight, and Mallory (1947) and Robinson (1933) have recorded that in some cases it is quite minimal. Inflammatory changes usually subside when cellular and humoral resistance overcome the pathogenicity of the infective process. A recent abscess cavity is thick-walled and surrounded by consolidated alveoli, but within a few weeks the wall is generally thin and at least comparable in thickness to that of pulmonary air cysts which have in the past been assumed to be congenital. The two most important causes of bronchiectasis and lung abscess are bronchial obstruction and infection. Bronchiectasis is predominantly a disease which occurs in childhood, and almost half of the cases of cystic disease of lungs collected in Schenck's review of the literature (1937) were under 15 years of age. Pulmonary infection is common in both the young and the old, but bronchial obstruction affects children more than adults because their bronchi are narrower and more easily occluded by a swollen mucosa, mucus plugs, or the external pressure of enlarged lymph nodes.

Bronchopneumonia principally involves the bronchi and surrounding tissue, and when the infection is staphylococcal, multiple abscess cavities sometimes result. In lobar pneumonia there is an extensive outpouring of inflammatory exudate which consolidates the parenchyma but the bronchi are much less affected. Valvular obstruction of the finer bronchi and bronchioles during the resolution of pneumonia leads to the rapid formation of pneumatocoeles either on the surface of the lobe or buried within its substance. These air cysts often contain inflammatory exudate, but as the infective process is on the wane when they occur there is little necrosis. With the absorption or expulsion of the material that occluded the finer tubes the pneumatocoeles usually disappear completely, but sometimes they are perpetuated by organic post-inflammatory bronchial stenosis.

It is impossible to tell radiologically whether cysts in the lung have started from a necrotic destruction of parenchyma by a lung abscess, or are due to the distension of small bronchi, bronchioles, or a collection of alveoli. Histological examination of the widened tubes in bronchiectasis generally shows a marked degree of destruction of the walls yet the eventual dilatations are elongated and in the general line of the former bronchi. A necrotic destruction of parenchyma, on the other hand, tends to spread centrifugally from some central focus, and after liquefaction and removal of the contents the resulting cavity is spherical. Bronchial epithelium relines the walls after the acute phase in bronchiectasis or a lung abscess, but the finding of other bronchial elements, such as muscle and elastic tissue, in the lining of some large cysts or in the walls of some bronchiectatic cavities suggests that ulcerative destruction of tissue was not a necessary stage in the formation of either.

The gross distension of a bronchial cyst, whether congenital or acquired, is likely to cause atrophy of the tunica propria, seromucous glands, cartilage, and surrounding alveoli. An intact bronchial stroma or fragments of it in the wall of a cyst has been taken as proof of a congenital aetiology, but this is unreliable for it has been demonstrated by the cases quoted here that cysts can develop and enlarge with practically no accompanying systemic reaction. The bronchi, bronchioles, or alveoli are distended into cavities by air pressure or exudate with little or no inflammatory destruction of tissue. The rapid dilatation of bronchi would cause distortion and scattering of the cartilage muscle and elastic tissue in their walls, and so finding clumps of these structures should not indicate a failure of normal formation originally. A congenital cyst of any structure in the foetus is invariably due to an impediment in the normal flow of body fluids. The dilated bronchial cavities observed in foetal lungs or portions of aberrant lung tissue are associated with bronchial obstruction, and it therefore seems reasonable to expect a similar obstruction in postnatal life to have the same effect. Congenital cysts have been considered a result of the failure of formation of alveoli and small bronchial tubes, but their absence in a morbid specimen can equally be accounted for by atrophy through compression by an enlarging cyst. Absence of carbon pigmentation in the parenchyma of some cases with cystic disease of the lungs is not conclusive of prenatal development, but implies that the cyst formed in

early infancy and impeded the respiratory function of the parts lacking the pigment.

Eloesser (1932) has made an extensive study of bronchial stenosis and noted that the result of stenosis depends on its site along the bronchial tree. A diffuse limitation of expiration, as found in asthma or valvular tracheal obstruction, produces a bilateral increase in lung volume. A valvular constriction of a bronchus to a lobe leads at first to over-expansion of the related parenchyma, but, as the obstruction to the expiration of air becomes more marked, alveolar collapse and dilatation of distal bronchi result. A similar valvular obstruction at bronchiolar level causes the alveoli to dilate and local emphysema. The latter is curiously localized, for some alveoli are hyperinflated while others are collapsed. Tannenberg and Pinner (1942), in their experimental work on rabbits, have shown that after complete bronchial obstruction pulmonary collapse occurs within about four hours, and in the absence of infection the distal bronchi are constricted. With infection beyond a block the distal bronchi rapidly become dilated with secretions, and may come to resemble a collection of sacs within a few days or weeks. They also recorded that alterations in intrapleural pressure did not affect the eventual formation of bronchial cavities.

Pulmonary collapse is common in childhood, yet is rarely complicated by the development of a lung cyst. Most pulmonary collapses are due to bronchial occlusion by mucus plugs created during bronchial inflammation, produced in asthmatic allergy or aspirated from the upper respiratory tract. When the collapse occurs there is usually a rise of body temperature for a day or two indicating some systemic infection. The rarity of cyst formation is not due to the small amount of intrabronchial material and its rapid clearance, because widespread rhonchi may persist for many days and the duration of a pulmonary collapse is measured in weeks. It is probable that mucus plugs, when they begin to loosen, are rapidly expelled or are softened to such an extent that they do not function well as check valves. For the production of a valvular mechanism, an organic stenosis formed by congested folds of mucosa or inflammatory constriction of the bronchial lumen may be necessary. Air is thought to permeate from aerated lung segments into collapsed ones through the interalveolar pores of Kohn, and aid in the expulsion of mucus plugs from small bronchi by the blast of air on coughing. It is possible that cysts occur during pneumonia because the interalveolar pores are blocked by exudate and do not relieve the air pressure behind a valvular obstruction.

Some children present with cysts in the chest, though they have no history of a severe pulmonary infection. It is not necessary to conclude that the cysts were formed by some mechanism in which inflammation was not a part, because in these days children are readily treated with antibiotics and chemotherapeutic drugs, often before the true nature of the complaint has been diagnosed. It is well known that fever and toxaemia in pneumonia rapidly respond to these drugs although the process of resolution still takes many days. The absence of a history of pneumonia cannot therefore be taken as evidence that the cysts in the child's lung were not the result of this pathology. It is possible, however, for cysts to form without any inflammation or obvious infection. An air-containing lung cavity can form after traumatic rupture of lung. In the adult asthma sufferer emphysematous bullae are common, and these occasionally occur in children and are seen as cyst-like translucencies on radiography. Over-distension of alveoli in an asthmatic person may also lead to cyst-like pockets of air in the interstitial planes through rupture of alveolar walls. Fibrosis of lung following past pyogenic or tuberculous inflammation is a cause of organic valvular bronchial stenosis and pulmonary cysts.

Allison (1947) has described large air cysts in adults, some of which were due to organic valvular stenosis and others to a small bronchial leak caused by a patch of ulcerative bronchitis. All his patients suffered from a cough, but few had had acute pulmonary infection, and the cysts showed a striking resemblance to the thin-walled cavities which occur in children. He noted that although the cysts looked like huge emphysematous bullae some of them were partly lined by cuboidal epithelium, and he made the interesting observation at operation on his cases that air entered a cavity with each forced expiration rather than during inspiration. If adults with relatively wide bronchi can develop stenosis and lung cysts it seems reasonable to suppose that children can do so with even greater facility because of the narrowness of the bronchi and the common history of a chronic cough over many months each year.

Material evidence of a congenital aetiology of lung cysts is rarely obtained, and it does not seem reasonable consistently to conclude that this has been destroyed by subsequent pulmonary inflammation. The observation in serial radiographs that cysts of lung can appear, enlarge, disappear, recur, or alter in number strongly supports the view that these pulmonary cavities are the result of an acquired pathology.

Summary

Cysts in the child's lung may be congenital or acquired. Very few have been recorded in stillborn

or newborn infants, but it has been generally assumed that most cysts are due to congenital malformation.

A number of lung cyst cases, observed over many years, are reviewed and the aetiology of the cysts discussed.

The conclusion is reached that most lung cysts are acquired as a result of bronchial inflammation and obstruction, and that very few are truly congenital in origin.

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HYPOPITUITARISM IN FIRST COUSINS

BY

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There is still much difficulty in elucidating the aetiological causes of dwarfism as it presents itself in children. After Erdheim in 1916 attributed dwarfism to a lack of pituitary secretion, it was for many years a common habit to implicate a pituitary deficiency in all dwarfs whatever their clinical features. A reaction to this unscientific approach was to be expected, and it has been so extreme in some quarters (Horstmann, 1950) that a pituitary origin for any type of dwarfism has been denied. Such a reaction is only possible if one contends that the enormous body of experimental work demonstrating the presence of an anterior pituitary growth hormone has no application to man, if one ignores the clinical pictures of dwarfism associated with destruction of the anterior pituitary, if one forgets the few reports of post-mortem examination in dwarfs which have demonstrated a deficiency of eosinophil cells in the anterior pituitary (Hewer, 1944), if one overlooks the clinical pictures of gigantism and acromegaly, and if one prefers not to remember that the absence of most hormones in the body is represented by a specific clinical syndrome. This aetiological nihilism, therefore, entails a denial of established fact which is too complete for most observers; but a moderate conservatism demands that some evidence of hypopituitarism should be forthcoming in any case of dwarfism before a diagnosis of pituitary dwarfism is made.

In the attempt to establish the aetiology of dwarfism in the individual child, all the systemic causes of infantilism and all the bone diseases which can produce short stature must be excluded. There are then two questions which urgently require an answer, Is this child suffering from hypothyroidism? Is there organic disease in the region of the pituitary? The clinical picture of cretinism is well recognized, but continued observation may be necessary to establish the diagnosis of juvenile myxoedema. If an arrest of growth can be shown not to be due to disease or malnutrition, then hypothyroidism should be suspected, and the signs of diminished vitality, cold extremities, slow pulse, electrocardiographic abnormalities, raised blood cholesterol level, and low basal metabolic rate must be looked for. Gross destruction of the pituitary by tumour, by xanthomatosis or by inflammation is rare in children, and a craniopharyngioma as a cause of dwarfism is very uncommon. When these infrequent causes are excluded, there remains a large group of children in whom a cause for their dwarfism has still to be sought, and among them will be examples of pituitary dwarfism.

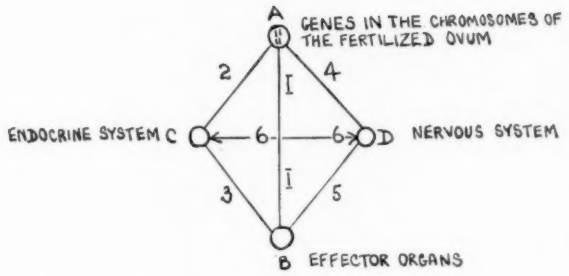
The separation of the cases of pituitary dwarfism due to the absence of the growth hormone would be simple if it were possible to assay the level of growth hormone in the blood or to determine the quantity of its metabolized products in the urine. However, no such investigations are as yet possible, and to determine whether dwarfism is related to a deficiency of the growth hormone, it is necessary to depend on a clinical picture of pituitary dwarfism, and to look for evidence of the absence of the other pituitary hormones. The gonadotropic hormones are excreted in small quantities before puberty. Until the age of puberty arrives, and the average time of onset may extend from 10 to 15 years of age in girls and 11 to 16 years in boys, it is not possible to support a diagnosis of pituitary dwarfism by the absence of gonadotropic hormones whether directly or indirectly.

The remaining two pituitary hormones are the thyrotropic and the adrenocorticotropic hormones. It is rarely possible to demonstrate any evidence of thyroid underaction in the absence of frank cretinism or myxoedema. Evidence of defective adrenocortical function should be sought in disturbances of carbohydrate metabolism, as in hypoglycaemia which may be due to a deficiency of the gluconeogenetic hormones of the adrenal cortex; in a disturbance of serum electrolytes together with

a positive Robinson-Power-Kepler test; and, as the age of puberty approaches, in the absence of sexual hair in both sexes and by a low output of 17-ketosteroids in males. It should be remembered, however, that such disturbance of carbohydrate metabolism may be associated with the absence of the growth hormone which inhibits the secretion of insulin in rats (Anderson and Long, 1947), thereby causing hyperinsulinism; that a disturbance of electrolytes can seldom be demonstrated in pituitary dwarfism; and that the signs of androgen deficiency are not apparent till puberty approaches. A deficiency of the anterior pituitary or the adrenal cortex may be demonstrated by Thorn's adrenaline-eosinophil test, while an adrenocortical defect may be detected by the absence of both the normal fall in the eosinophil count, and the normal rise in the urinary uric acid/creatinine ratio after 25 mg. of ACTH.

It is probable, however, that deficiency of the growth hormone may occur alone and in the absence of coincident deficiency of the other anterior pituitary hormones. This observation is supported by some clinical evidence, but also by an occasional pathological report. Hewer (1944) recorded an extensive necropsy examination in a woman aged 76, whose height was 3 ft. 11 in. and who had borne one child, and in the anterior pituitary of this dwarf he demonstrated an almost complete absence of eosinophil cells. In a child, therefore, in whom dwarfism exists before the age at which the sex hormones can be expected to be active, or in whom dwarfism continues after puberty, there usually remains a considerable diagnostic problem as to the aetiology of the dwarfism. Other causes of dwarfism, both constitutional and genetic, must then be considered before a firm diagnosis of pituitary dwarfism can be made. In dwarfs in whom epiphyseal development occurs at the average age it appears improbable that an absence of the growth hormone can be implicated. Where an absence of the growth hormone can be assumed, epiphyseal development will show moderate retardation. The group with normal epiphyseal development will include the so-called ' primordial ' dwarfs who occur sporadically in families whose members are of normal height; it will also include children of inherited short stature.

It is useful to recall Bauer's (1943) diagram which illustrates the aetiology and pathogenesis of developmental disorders. Disturbances of growth may be caused in A (' a mess in the chromosomes '), in C (pituitary, thyroid, adrenal, or testis), in B (skeletal disorders or diminished sensitivity of end organ), and in D (hypothalamus) while they may be mediated through paths 1, 2, 3, 4, and 5.



It must be assumed that the ' primordial ' dwarfs grow to a height genetically determined; whether or not these primordial dwarfs are an example of a diminished sensitivity of the end organ, in this case all the somatic tissues, in the presence of normal or increased amounts of the specific hormone, cannot be decided in the absence of assays of the growth hormone. The most commonly occurring example of the primordial dwarf is the so-called Lorain dwarf. Here the height age is less than in hypopituitary dwarfism, but the bone age is within average limits. In other respects, except in a failure to grow, development is perfect and there is no persistence of the infantile facial appearance. The group of genetic dwarfs also includes those girls and women who suffer from ovarian agenesis in association with other congenital defects. In the group of dwarfs showing delay of epiphyseal development and fusion (hypothyroidism already excluded) are the pituitary dwarfs and also children whom Wilkins (1950) described as showing delayed adolescence. This last group show a consistent delay of two to four years in their epiphyseal development, and in their early 'teens fail to show the normal spurt in growth and sexual development. The spurt comes at a late age, and they may never attain average height. It appears probable that this is a heterogeneous group, in some of whom the peculiar pattern is genetically determined, while in others the delayed growth is the result of environmental factors. In either case, the delayed epiphyseal development may indicate relative deficiency of the growth hormone or diminished sensitivity of the skeleton to its stimulus. The genetic cases may be associated with a disturbance of the normal growth hormone: androgen ratio.

Talbot (1945), and Talbot, Sobel, Burke, Lindemann, and Kaufman (1947) have suggested that malnutrition, sometimes resulting from emotional anorexia, may be an environmental factor in the defective formation of the growth hormone.

In our present state of diagnostic inadequacy, any evidence which supports a diagnosis of pituitary dwarfism is therefore valuable. The description follows of two boys who were first cousins, born of

FIG. 2.

FIG. 2.—T.B. Note immature facies.

FIG. 1.—T.B., aged 7½ years, height 37½ in., photographed with boy of the same age.

FIG. 1.

two sisters, whose husbands were unrelated to each other or to their wives. The boy, aged 7½ years when first seen, showed the clinical picture of pituitary dwarfism, and his male cousin, aged 20 years, showed hypogonadism with a eunuchoid habitus, delayed epiphyseal fusion, osteoporosis, and deficiency excretion of urinary gonadotropins.

Case Reports

Case 1. Terence B., aged 7½ years (Figs. 1 and 2), weighed 7 lb. at birth. He developed normally during the first two years of his life, reaching his milestones at an average age. His mother did not notice that he was not growing naturally until he was 2 years old. He was then treated by thyroid tablets for two years, but no improvement in growth occurred. He was taken to another city where he was given other treatments without success.

His mental age was within average limits and he was doing reasonably well at school.

He had had pertussis and measles but no other infectious diseases.

All the members of the family are of normal growth and sexual development, except Terence's first cousin D.T. described below.

On examination Terence B. proved to be an alert, happy child, with normal functions and with a good appetite. The facies shows an infantile naso-orbital configuration. The skin was not pale, and the extremities not cold. His height was 36½ in. (normal approximately 47½ in.). The span was 35 in. The height age was less than 3 years. His weight was 30 lb. (normal approximately 50 lb.). The upper segment was 19 in., the lower segment 17½ in., and the ratio of the segments 1·1:1 (normal 1·1:1). The head circumference was 19½ in., the chest circumference 19½ in.

A radiograph of the bones showed that the pituitary fossa was normal. There was no epiphyseal dysgenesis. All bones of the carpus (except the pisiform), and the head of the radius and patella were present. The distal epiphyses of the ulna (Fig. 3) and internal epicondyle of the humerus were absent. Bone age was therefore between 5 and 6 years.

The insulin sensitivity test (Fig. 4) showed a normal sensitivity with some lack of hypoglycaemic response:

Fasting blood sugar ..	100 mg. %
15 minutes	60 mg. %
30 minutes	60 mg. %
60 minutes	60 mg. %
90 minutes	70 mg. %
120 minutes	75 mg. %

The blood count was normal. W.B.C.s were 11,600 per c.mm. (eosinophils 3%). The response of eosinophils to 0·3 mg. adrenaline was not abnormal.

The blood cholesterol level was 281 mg. %. This was repeated one month later (not after thyroid therapy) and was then 241 mg. %.

The electrocardiogram was normal.

The Wassermann and Meinicke reactions were negative.

The Mantoux test (1 in 1,000 O.T.) was negative.

The urinary hormonal excretion (Dr. A. M. Hain) showed urinary 17-ketosteroids 3·9 mg. in 24 hours.

All other investigations, both radiological and biochemical, gave normal results.

In view of Terence B.'s high blood cholesterol level and despite the absence of any other signs of hypothyroidism, he was treated for three months by thyroid therapy. There was no acceleration of growth

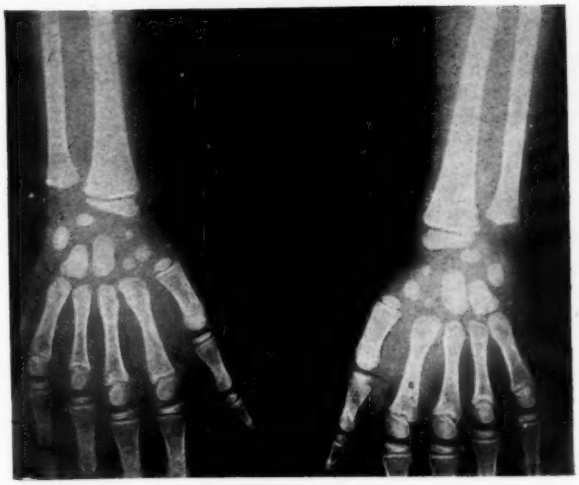


FIG. 3.—Radiograph of carpus of T.B.; note absence of ulnar epiphysis which normally appears at the age of 6 years.

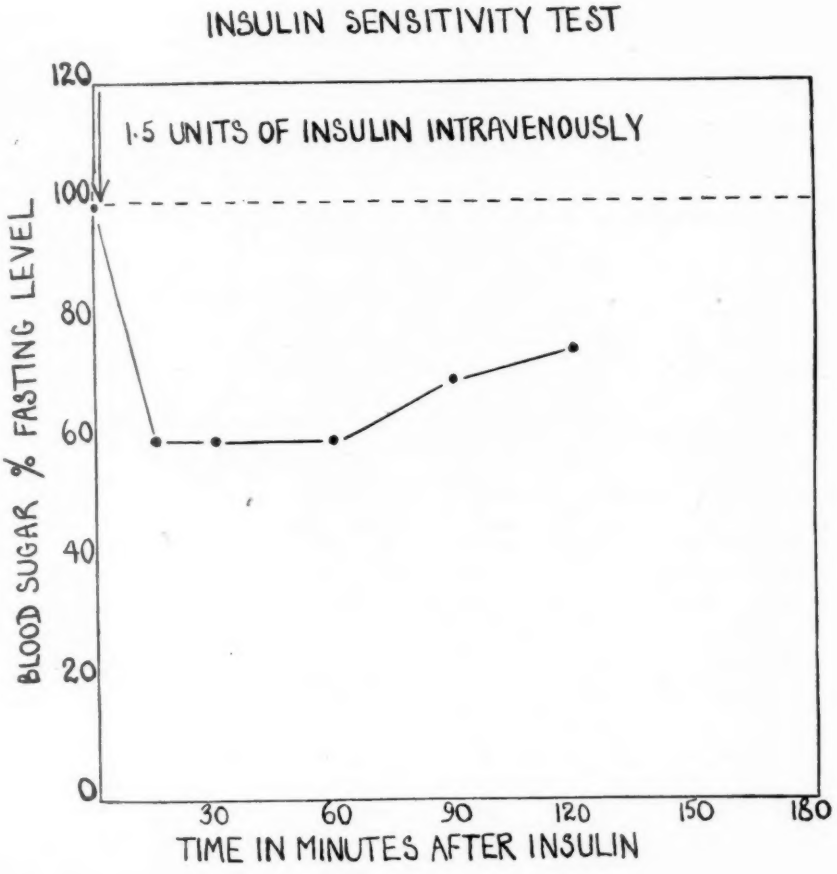


FIG. 4.—Insulin sensitivity curve (reaction to hypoglycaemia of T.B.). This shows a normal insulin sensitivity but with some lack of hypoglycaemic response. The blood sugar levels are expressed in the curve as a percentage of fasting level. (This and the subsequent tests were made with intravenous insulin, 0·1 of a unit per kg. of body weight.)

and no advancement of bone age. He was then treated for three months by growth hormone, 'antuitrin-G' (Parke Davis), with no improvement. For a further three months he was given 'amdinon' (Organon), a preparation of thyrotropic hormone with growth hormone; this also produced no appreciable growth. During the next three months he was given methyltestosterone therapy and grew 1½ in. in this period.

Case 2. D.T., first cousin to T.B., aged 20, has never shaved, and his voice is said to have become no deeper since his childhood. He had had no penile erection and no seminal emission before admission to hospital. He was referred to the hospital for treatment of varicose veins.

The family history shows that there were no siblings in the family. Both father and mother are of normal growth and sexual development.

FIGS. 5 and 6.—D.T. Note disproportionate length of limb and wide hips.

On examination the patient's weight was 9 st. 2 lb.; his height 5 ft. 7 in. The span was 5 ft. 11 in.; the upper segment was 31 in., the lower segment 36 in., and their ratio 0·86:1. The body was of feminine type with wide hips (Figs. 5 and 6). There was sparse axillary and pubic hair, and no hair on the face. Both testes and penis were much smaller than the average for an adult male. He had genu valgum with pes planus, and there were varicose veins in both legs.

The dermatological report (Dr. P. D. C. Kinmont) showed mild xeroderma of the legs and face with a probable allergic eczema on cheeks, forehead, arms, and ankles. He had very lax joints, particularly in the feet, with curious circular scars on the legs and feet. The appearance was suggestive of the scars of epidermolysis bullosa. There was no cutis laxa hair. He had a tendency to bruising, and there was capillary dilatation on the legs. No other abnormal sign was discovered on clinical examination in any other system.

Investigation gave the following results: serum calcium level 10·4 mg. % (after calcium and testosterone therapy 11·8 mg. %); serum phosphorus level 5·0 mg. %; alkaline phosphatase level 5·2 units; serum proteins 7·6 g. % (serum albumin 4·4 g. %, and serum globulin 3·2 g. %).

The insulin sensitivity test (Fig. 7) gave the following results:

Fasting blood sugar	100 mg. %
30 minutes	60 mg. %
60 minutes	80 mg. %
90 minutes	80 mg. %
120 minutes	90 mg. %

No excess of fat was found in the chemical examination of a three-day specimen of faeces.

Analysis of urinary 17-ketosteroids (Dr. A. M. Hain) gave: on June 16, 1950, 10·2 mg. in 24 hours; on June 26, 1950, 9·1 mg. in 24 hours. After two months' methyltestosterone therapy, on August 27, 1950, excretion was raised to 14·0 mg. in 24 hours. The urinary gonadotropins on May 16, 1950, were less than 6 M.U. in 24 hours; on June 18, 1950, they were 2 M.U. in 24 hours.

Radiographs after a barium meal showed a normal small intestine pattern. The pituitary fossa was normal in outline; there was generalized osteoporosis of the skeleton (Fig. 8), and a marked delay of epiphyseal fusion with a bone age of 17 to 18 years (Fig. 9).

The blood count was normal. Eosinophil polymorphs were 5% of 8,200 W.B.C.s per c.mm. The response of eosinophils to adrenaline (0·3 mg. subcutaneously) was not outside normal limits.

A testicular biopsy (Dr. G. R. Osborn) showed that the seminiferous tubules had a normal basement membrane (Fig. 10). The cells were nearly all of the Sertoli type. Small numbers of early sex cells (spermatogonia) were present, but very few had mitotic figures and no differentiation to later types was seen. The spermatogonia had much larger nuclei than the Sertoli cells. In the interstitial tissue there appeared to be a total absence of Leydig cells. This was in striking contrast to the atrophic undescended testis. Treatment by chorionic gonadotropins produced no increase in the size of the testes.

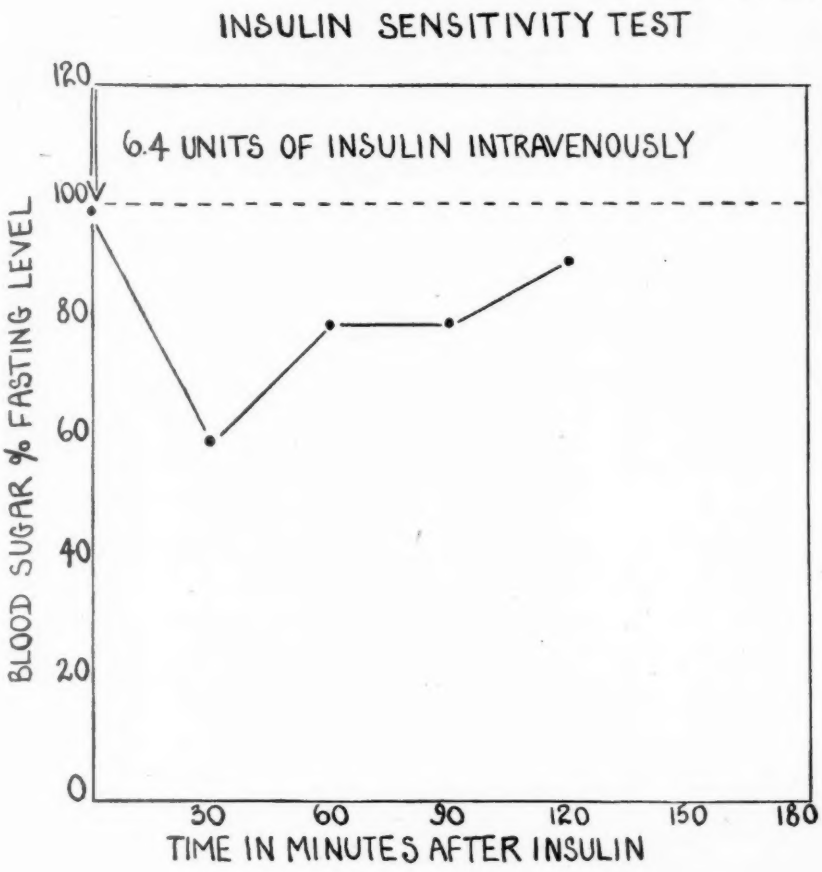


FIG. 7.—Insulin sensitivity curve (reaction to hypoglycaemia of D.T.).

FIG. 8.—Radiograph of lumbar spine of D.T. showing osteoporosis.

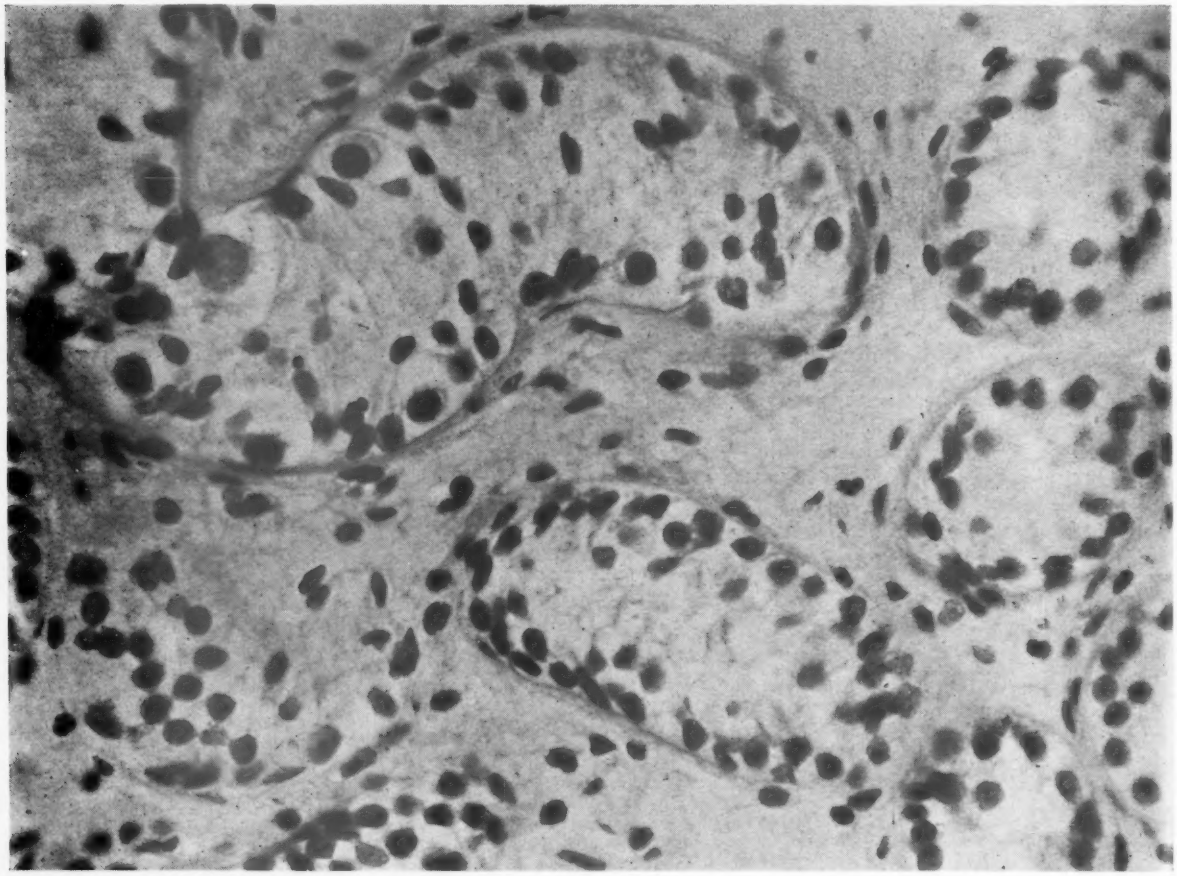
FIG. 9.—Ulnar epiphysis of D.T. not yet united.

FIG. 10.—Photomicrograph of biopsy of testis of D.T. × 900.

Treatment by methyl-testosterone (20 mg. b.d.) caused increased growth of axillary and pubic hair. The facial hair grew, and it became necessary for the patient to shave once a week. The penis increased in size, but the testicles showed no alteration in size. He had occasional erections, but no seminal emission as a result of treatment. His voice deepened and both his habitus and his outlook became more masculine.

Discussion

The boy T.B., aged 7½ years, showed the clinical appearance of a pituitary dwarf, but the diagnosis of pituitary dwarfism should not be considered probable unless (1) cretinism or myxoedema is excluded, (2) the height is at least 20% below the average for coevals, (3) the bone age, after the age of 5 years, is at least two years behind coevals, (4) the ratio of upper to lower segment corresponds approximately to the 'chronological' age (proportionate dwarf), and (5) the features are immature. If these criteria are present, then it is justifiable to assume that the dwarfism is hypopituitary in origin whether the defect is congenital or conditioned. It may well be that growth retardation of lesser



degrees may occur with partial deficiency of the growth hormone, but this cannot be established in the absence of evidence of deficient production of anterior pituitary hormones whether before the age of puberty or after. It has been postulated by some observers that the absence of growth hormone produces defective bone growth by conditioning an absence of thyrotropic hormone, while others have suggested that there are reasons for thinking that the dwarfism of hypothyroidism may be due to a conditioned deficiency of growth hormone. These theories are speculative, and as a rule in pituitary dwarfs there is no evidence of hypothyroidism, a diagnosis which in children can be made with considerable exactitude. In T.B. there was no evidence of hypothyroidism except for a raised serum cholesterol level, and growth was not accelerated by thyroid therapy. A clinical diagnosis of pituitary dwarfism in T.B. is supported by finding hypopituitarism in his first cousin, D.T., with evidence of hypogonadism (testicular hypoplasia), eunuchoid habitus, and osteoporosis with delayed epiphyseal fusion.

The diagnosis of hypopituitarism in D.T. is confirmed by the low gonadotropin urinary excretion (less than 6 M.U. while the normal is 6-50 M.U. in 24 hours). The excretion of 17-ketosteroids (9-10 mg. in 24 hours before testosterone therapy) represents the normal product of adrenal androgens. The scarcity of Leydig cells in the testis gave histological support to the clinical diagnosis of absent testicular androgens (representing one-third of the 17-ketosteroid excretion) as evidenced by the eunuchoid habitus (low upper to lower segment ratio and span greater than height), the sparseness and absence of sexual hair, the delayed epiphyseal fusion and the generalized osteoporosis. Osteoporosis of the degree seen in D.T.'s skeleton is rare in hypopituitarism, although it is well explained by the absence of testicular androgens (Albright and Reifenstein, 1948). In their absence there is a defect in the deposition of osteoid tissue while resorption of bone proceeds normally.

The insulin sensitivity test was normal in both subjects, except that in T.B. there was some diminished response to hypoglycaemia. Although this was shown to be present in subsequent tests, it is doubtful if it can be interpreted as evidence for the absence of an anti-insulin factor (? growth hormone).

The purified growth hormone causes neither nitrogen retention in normal individuals nor does it enhance growth in pituitary dwarfs (Bennett, Weinberger, Escamilla, Margen, Li, and Evans, 1950) and yet no inhibitors to its action in the blood were demonstrated by these observers. The most probable explanation is that in man it requires some catalyst as yet undetermined for its effective action. It would be premature to use the failure of the growth hormone in therapy as an additional argument against a hypopituitary aetiology for dwarfism in man.

Treatment by thyroid therapy, by thyrotropic hormone and by growth hormone ('antuitrin-G" Parke Davis) in T.B. produced no result; treatment by chorionic gonadotropins in D.T. produced no enlargement of the testes. Treatment by methyl-testosterone in T.B. caused acceleration of growth, while in D.T. increased density of bone and growth of sexual hair could be demonstrated after methyl-testosterone therapy. In D.T., since chorionic gonadotropins failed, treatment by methyl-testosterone was indicated. It will develop the secondary sexual characters of the male, and it will retain nitrogen and calcium and increase the density of bone. It has been suggested by Talbot *et al.* (1947) that methyl-testosterone will stimulate the anterior pituitary, and there is evidence that this effect was achieved in D.T., for after two months' therapy with methyl-testosterone the excretion of urinary 17-ketosteroids increased from 10 to 14 mg. in 24 hours. Testosterone in the experimental animal inhibits both the gonadotropic hormones and ACTH without affecting the thyrotropic hormone, but these effects may be altered by a change of dosage. Since there is no therapeutic preparation of the follicle stimulating hormone and lateral hormone, there is no possibility of stimulating the testis by any other means.

The advisability of the treatment of pituitary dwarfism in children before puberty by testosterone is debatable. The arguments against it are that the testes may thereby be damaged, and that the ultimate height of the child will not be increased by such therapy. It is possible to damage the testis after puberty by testosterone therapy, but there is no evidence that this occurs before puberty. In men after daily doses of 25 mg. of testosterone propionate over long periods (24-91 days) it has been shown that the testicular changes are completely reversible (Heller, Nelson, Hill, Henderson, Maddock, and Jungck, 1950). There is one biopsy report in the literature (Talbot, 1945) in which testosterone was administered to a boy in interrupted courses between 13 and 16 years of age, and testicular biopsy at 16 years showed no evidence of damage. There can be no proof that testosterone will not increase the ultimate height of a pituitary dwarf. Providing it is not used in children whose bone age is normal (e.g. non-pituitary dwarfs), and providing the child's bone age is not accelerated beyond the normal for its age, it seems reasonable to employ

testosterone in therapy, using it in interrupted courses, and with adequate radiographical control.

Summary and Conclusions

The difficulties of distinguishing pituitary dwarfs before the age of puberty from the other types of dwarfism—whether 'primordial,' genetic or acquired—are considered.

Criteria are suggested for the clinical diagnosis of pituitary dwarfism of which the most important are the persistence of an immature facies, the retardation of bone age by at least two years, and a height which is at least 20% below the average for coevals in the proven absence of hypothyroidism.

Two male first cousins are described, in one of whom, aged 7½ years, pituitary dwarfism was present and in the other, aged 20 years, pituitary hypogonadism, with deficient urinary excretion of gonadotropins, testicular hypoplasia, eunuchoid habitus, defective secondary male sexual characters, osteoporosis with retarded union of epiphyses, could be demonstrated.

It is suggested that when other treatments have failed it is justifiable to use methyl-testosterone therapy after the age of puberty in pituitary hypogonadism, and before the age of puberty in pituitary dwarfism. In the latter case care must be exercised not to advance the child's bone age beyond the chronological age so that early epiphyseal closure is avoided.

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OBESITY IN A CHILD

BY

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The following case is reported for two reasons. In the first place, the patient exhibits in an unusually distinct manner the factors which appear to underlie most instances of obesity in childhood, and secondly it was possible to detain a cooperative and intelligent patient in hospital for long enough to conduct a simple experiment which does not seem to have been recorded previously.

Case Report

The patient was a girl of 11 years who was referred because of obesity. She was the last of four children, of whom one had died in infancy. The dates of the births of the children were: 1923, 1926, 1929 (this child died at the age of one month), and 1939. The mother's age at the time of the girl's birth was 41 years. The gap of 10 years between the third and fourth pregnancies, the fact that the third child had died in infancy, and the patient's arrival at the end of her mother's reproductive life, all contributed to make her an object of special regard from the day of her birth. In the mother's words: ' she always had special care taken of her '.

Her sister was plump, but not excessively stout. The brother was said to be thin. The mother stated that she herself had been very stout until the age of 14 when she had lost much of her excess weight. At the time of interview she was certainly overweight but not grossly obese. The maternal grandmother was said to have been stout, but the male members of the family on both sides were reported to be slim.

The child weighed 7 lb. at birth, and was said then to have been normal. Breast-feeding was continued for nearly two years, and solids were not successfully introduced until the age of 18 months. The mother stated that she had made repeated attempts to discontinue breast-feeding after the first year, but the child insisted on having the breast even when she was taking adequate meals.

No record of weights was kept, but the mother reported that from about the age of 3 years the child began to gain weight rapidly and that the excessive gain in weight had continued since then. Her mental development was apparently normal. She went to school at the usual time and had maintained average progress. Physically she had appeared normal apart from the obesity and a deformity of the right foot. She had had the usual infectious fevers without sequelae and an appendicectomy in December, 1949.

The whole family were said to be ' good eaters '. The mother, on direct questioning, admitted that the girl ate as much as the adult members of the family. She would eat large amounts of any food offered, but had a special predilection for starchy foods. She usually ate four slices of bread at a sitting, and would take six or seven large potatoes as a helping; fried chipped potatoes were her special weakness. In the family these eating habits were regarded as normal. Her fluid intake was not excessive.

The deformity of the foot which prevented her playing games has already been noted. She was said to avoid other children, and on return from school she remained indoors engaged in a variety of sedentary occupations such as reading, knitting, etc.

When she was examined on admission to hospital she was seen to be very obese (Fig. 1 A). She weighed 132 lb. and was 58 in. tall. That is, she was approximately 70% overweight, but within the normal limits of height for her age. The fat showed no unusual distribution. There was no pitting oedema of the legs. The skin was dull, but there was no hirsutism or abnormal coloration. Breast development was apparent, but the large deposits of fat made the true size of the breasts difficult to decide. There was no pubic hair, and she had not menstruated. Hallux valgus of the right great toe was present. Otherwise examination revealed no abnormality. Her blood-pressure was 105/70 and the optic discs were normal.

Mentally she was a quiet, shy, withdrawn child who spoke little and in a low voice. She appeared to be mildly depressed and spontaneous movements were few. Her intelligence was better than average. (No tests were performed, but the school-teacher who visited the ward considered that her performance in set tasks was above average.) The general impression she gave was of a rather pathetic, discouraged child, conscious of her ungainly appearance, who tended to isolate herself.

The following investigations gave essentially normal results: urine analysis, full blood count, examination of the faeces, glucose tolerance test, blood cholesterol and

serum protein levels, radiographs of the ulnar epiphyses to determine bone age and of the skull for size of the pituitary fossa.

She was assessed as a case of simple obesity without endocrine or other abnormalities.

Five days after admission to hospital, she was started on a diet of 1,150 calories, containing 100 g. of carbohydrate, 70 g. of protein, and 50 g. of fat. Salt was withheld during cooking and at table. She continued on this diet for the duration of her stay in hospital. She was a most cooperative patient whose conduct was exemplary and whose anxiety to lose weight became very manifest.

On the twentieth day in hospital an operation to correct the deformity of the toe was performed and just before and after this she was confined to bed for 15 days. Otherwise she was up for most of the day and became a useful helper in the ward.

Her intake of fluids and her urinary output were measured from the date of admission. In the first period no restrictions were imposed, and she was allowed to drink when she liked and as much as she wished. The purpose was to determine her usual intake of fluids, and her rate of loss of weight on this intake on the basal diet. This period lasted for 44 days, but the fluid measurements were discontinued for the period during which she was confined to bed. Thus figures are available for 29 days. During this period her average daily intake was 29 fluid oz. (maximum, 45 oz., minimum, 20 oz.).

FIGS. 1A and 1B.—The child on admission (1A) and after the experiment (1B).

At the end of this period she was asked to drink as much water as she could without discomfort; this forced intake was continued for eight days. Thereafter she was requested to restrict her intake of fluids to the minimum she could manage without discomfort; this was continued for six days. At the end of this time she was again asked to drink to capacity. These alternating periods of restriction and excess were continued for a total of 41 days. The variability of intake was very marked. The average intake in the periods when she was drinking as much as she could was 92 fluid oz. (maximum, 127 oz., minimum, 41 oz.), and during the periods of restriction only 15 oz. (maximum, 21 oz., minimum, 10 oz.).

She was weighed daily in the same clothes, at the same time, and after emptying her bladder. The weight curve during the preliminary period of observation showed the usual fluctuations encountered in obese persons on a reducing diet (Newburgh, 1944; Evans, 1947), but over the whole period there was a loss of 10 lb. 8 oz., i.e. an average daily loss of just under 4 oz.

The results during the controlled periods are shown graphically in Fig. 2. Urinary outputs are shown at the top, the weight curve in the middle and the fluid intakes at the bottom. The + signs indicate days when the urinary output exceeded the fluid intake. The continuous thin line under the weight curve is the 'expected weight loss,' i.e. the weight loss which would have been anticipated on the basis of the rate of loss during the period of uncontrolled fluid intake. The vertical lines indicate the points of change from excessive intake to restricted intake and vice versa.

The effect of the greatly increased fluid intake is apparent in the tendency of the weight curve to flatten out or even to rise during the first five or six days of each period. This is associated with a marked discrepancy between urinary output and fluid intake, most noticeable in the third period. On the sixth or seventh day, however, the weight showed a tendency to drop, and the urinary output increased. Taking the three periods together there was, during the first five days of excessive intake, an average *gain* in weight of 1½ oz. per day; on the sixth and seventh days there was contrarily an average loss of 4 oz. per day.

When the intake was restricted there was first a dramatic reduction in urinary output. This was followed by a diuresis in spite of the continued restriction, i.e. by an excess of urinary volume over daily intake. The weight loss was not constant or regular, but in the first three days the average loss was 10 oz., and in the second three days 5 oz. per day.

At the end of the experiment the child weighed 112 lb. 4 oz. She was much more cheerful and sociable (Fig. 1B).

After discharge she has been seen several times as an out-patient and has continued to lose weight, though at a slower rate, on a rather less restricted diet. The change in her attitude is marked. Now, on returning from school she hurries out to be with her friends; she is most particular about her diet and is interested in her appearance in an active healthy fashion.

Comment

The factors concerned in the genesis of this girl's obesity appear to be the following: (1) a familial tendency to plumpness of the females in the family; (2) restricted physical activity, due in part to the deformity of the foot, but even more to a feeling of insecurity with other children; and (3) faulty eating habits, primarily due to over-zealous parental care.

The three basic factors may be termed genetic, physical, and psychological. Of these the last appears to be the most important, since it accentuates the rather small effects of the other two and leads directly to the major cause of the obesity, viz. overeating.

The factors which, it seems safe to assume, are not concerned are an endocrine upset, of which there is no evidence of any sort, and water retention.

It is clear that during the early part of the periods of forced intake there was a certain amount of water retention. However, as the decrease in weight at the end of these periods, associated with a marked increase in urinary volume, show, this was a self-limiting process.

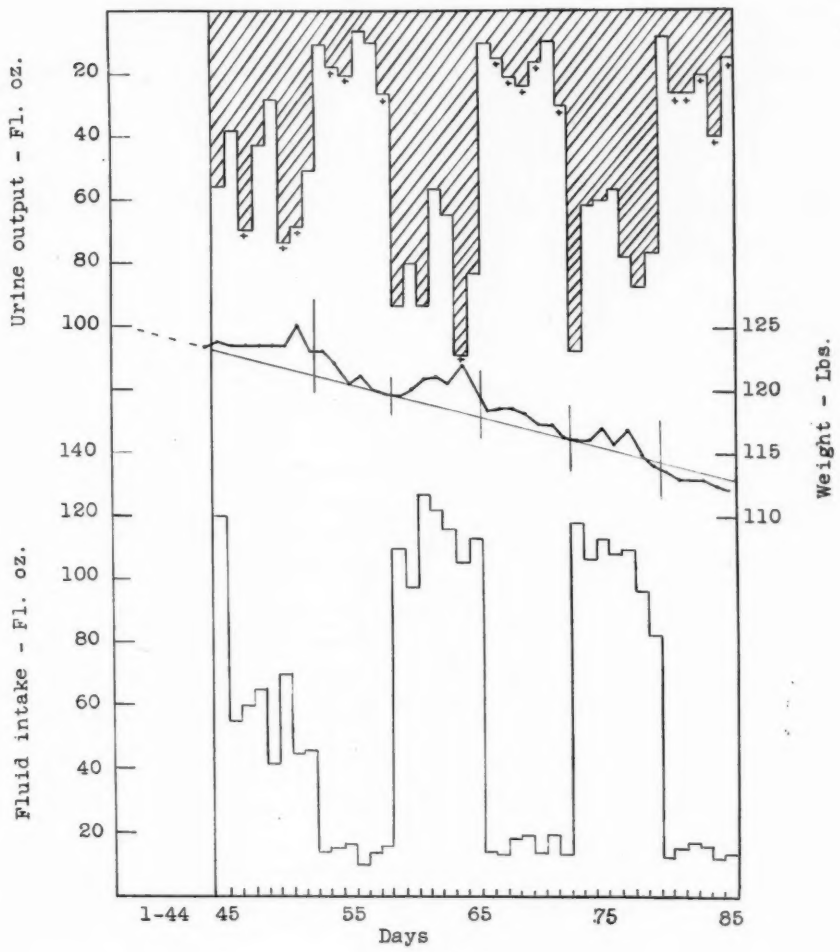

FIG. 2.

The capacity of adipose tissue to retain water is well known. It is a phenomenon which in some countries has been of economic importance, since the ability of the camel to go for prolonged periods without water is dependent on its possession of a portable reservoir in the form of its hump. Grafe (1933) reports that the fluid content of human fat has been found by several investigators to vary from 5% to 71%. He states that 'fatty tissues absorb water like a sponge, without circulatory disturbances and with no evidence of oedema.' The curious phenomenon by which this retained water is held in the tissue with great tenacity during periods of undernutrition has been repeatedly commented on (Grafe, 1933; Newburgh, 1944; Evans, 1947; Greene, 1948). Wiley and Newburgh (1931) have shown that this occurs in normal individuals during periods of starvation. Grafe says that 'every undernutrition leads to retention of fluid,' and Newburgh concluded from his experimental data that 'excessive retention of water is seen to be merely a by-product of undernutrition. It in no way indicates that the metabolism of obese persons is abnormal.'

In the present case it was found impossible to achieve a persistent gain in weight on intakes of water which were on the average more than three times the normal consumption, and such water as was stored on these excessive intakes was very readily excreted during the periods of restriction. It seems improbable that on her usual intake this child stored water to any appreciable extent.

This patient illustrates very clearly the importance of Bruch's (1940) demonstration that in a large number of cases of childhood obesity, food has a special significance in the parent-child relationship, and that the excessive consumption often represents

a search by the child for comfort which it does not find in other ways. The most striking feature of the present case was the marked change in the girl's attitude to herself and her environment. This was due to three things: the indubitable demonstration that she could lose weight and remain well; the close contact with other children in the ward; and the constant interest in her progress displayed by the medical and nursing staff. She ceased to be the timid child afraid of giving up the breast and became a real person, able to control her environment with reasonable success and assurance.

Summary

The case of a girl with marked obesity is reported in which an attempt to demonstrate water-retention was made during a period in hospital. The results indicate that on very large fluid intakes a small amount of water-retention occurred, but that this stored water was easily removed by restriction of fluids. It seems unlikely that in this case water storage played any important part in determining the child's bulk. The most important factors, both in aetiology and in treatment, were psychological.

Dr. D. V. Hubble who was in charge of the case gave permission for the experiment to be performed and for publication of this report. Sister B. Wilson supervised the fluid measurements. To both I wish to express my thanks.

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THE RADIOLOGICAL "DOUBLE CONTOUR" EFFECT IN THE LONG BONES OF NEWLY BORN INFANTS

BY

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The radiological appearance of a double contour on the sides of the long bones of infants has been noted by several writers since Chiari first drew attention to it in 1938. Many theories of its causation and significance have been advanced, including the view that it may be due to organic disease such as rickets or syphilis. Glaser, however, in 1949 suggested that this appearance may be seen in radiographs of normal, healthy bone, and that its production depends on the angle of projection. The results of the investigation described below support his view that a double contour effect may be seen in normal bones, but suggest that its origin is in the histological structure of the bone itself rather than in the technique of radiography.

Investigation

One hundred and seventeen infants, of whom the majority were premature, born in the Mill Road Maternity Hospital, Liverpool, have been studied, 97 during life and 20 after death. Of the living infants, 73 were regarded as healthy, 62 being premature, with birth weights of 5 lb. 8 oz. or less, and 11 mature. Twenty-four were abnormal on account of congenital defects or acquired disease.

Each infant was examined physically while in hospital and subsequently after discharge. All were radiographed before discharge from hospital, the mature infants usually during the second week, and the premature infants when the weight reached 5 lb. in the breast fed, and 5½ lb. in those artificially fed. The radiographic examination included antero-posterior and lateral projection of the limbs, with oblique and tangential views when required. A rotating anode tube with a 1 mm. focal spot and non-screened films were used. The focal-film distance was usually 40 in. with KV 55, and Mas. 20.

Results

A double contour effect was noted on the radiographs of the long bones as a single, continuous, linear shadow running adjacent to the diaphysis on its outer side, and separated from it by a radio-translucent strip about 1 mm. in width (Figs. 1, 2, 3, 4). This thin, pencilled line, which was never laminated, was limited to the diaphyseal portion of the bone, and never extended beyond the metaphyseal region, at which point it merged with the outline of the diaphysis. It was somewhat variable in its extent and position, being visible on both sides of some bones and on only one side of others. In some it extended the whole length of the diaphysis while in others it was limited to a part of the shaft. Commonly, though by no means invariably, it was present in both limbs. In some cases it was very obvious, in others it had to be looked for carefully. Variation in the focal-film distance or in the angle of projection of the radiographs produced no difference in the appearance of the double contour.

Healthy Infants. The 73 healthy infants showed no physical signs of organic disease while under observation. Blood alkaline phosphatase estimations in three revealed values within the normal range for infants (25, 22, and 27 King Armstrong units), and in one the serum calcium level was 12·5 mg. and the phosphorus level 5·1 mg. per 100 ml. The mothers of all these infants were also regarded as healthy, and had negative blood Wassermann reactions and/or Kahn tests.

The double contour effect was noted in one or more bones in 20 (27%) of the 73 cases examined. Of these 14 (70%) showed the appearance in more than one bone. The bones most commonly affected were the tibia and ulna, followed by the fibula, radius, femur, and humerus. No double contours

were seen in the ribs, clavicles, metatarsals, metacarpals, or phalanges.

The incidence of the double contour effect in individual bones is shown in Table 1.

TABLE 1
INCIDENCE OF THE DOUBLE CONTOUR EFFECT IN INDIVIDUAL BONES

Bone	Number of Infants Showing Double Contour	Percentage
Tibia ..	15	22
Ulna ..	14	20
Fibula ..	9	12
Femur ..	7	10
Radius ..	7	10
Humerus ..	2	3

The incidence of the double contour effect in combinations of bones in the same patient is shown in Table 2.

TABLE 2
INCIDENCE OF DOUBLE CONTOUR EFFECT IN COMBINATIONS OF BONES IN THE SAME PATIENTS

Combination of Bones	Number of Infants Showing Double Contour	Percentage
Radius and Ulna ..	8	11
Tibia and Fibula ..	6	8
Tibia, Fibula, Radius, and Ulna ..	2	3

The incidence of double contour effect in infants of varying maturity at birth is shown in Table 3 where the infants are divided into groups according to their birth weights. The high incidence of the effect in the infants of lowest birth weight is striking.

Amongst the healthy infants were four pairs of twins, two uniovular and two binovular. In one of the uniovular pairs both infants showed double contour effect, in the other it was well marked in one infant, but absent in the other. Of the binovular twins the effect was noted in both infants of one pair and in neither infant of the other pair.

Radiographs taken at intervals revealed that the length of time the double contour effect persisted varied from infant to infant, remaining in some for one month, in others for longer periods up to eight months after the initial radiograph. As a rule, the more pronounced the change initially, the longer it persisted. We did not note its reappearance in any case serially radiographed, though such an occurrence would be quite compatible with our histological studies. Nor did we see its later development as described by Glaser in infants whose initial films did not show the change.

TABLE 3
INCIDENCE OF DOUBLE CONTOUR EFFECT AT DIFFERENT BIRTH WEIGHTS

Birth Weight	Number of Infants Showing Double Contour	Percentage
Under 3 lb.	5	80
3 lb.-3 lb. 15 oz. ..	26	42
4 lb.-4 lb. 15 oz. ..	27	26
5 lb.-5 lb. 7 oz. ..	5	20
5 lb. 8 oz.-5 lb. 15 oz.	3	None
6 lb. and over ..	7	None

Abnormal Infants. The double contour effect was noted in two (8·4%) of the 24 abnormal infants included in the investigation.

Of these infants, six had congenital deformities, eight suffered from haemolytic disease, two showed radiological evidence suggestive of rickets, and five, with their mothers, had positive blood Wassermann and Kahn reactions. The double contour effect was seen in two of these five infants. It was not observed in the other 22 cases.

The congenital deformities were anencephaly, encephalocoele, lacunar skull, spina bifida, achondroplasia, and dyschondroplasia. The radiographs of the bones in these cases revealed the appearances characteristic of the deformities. The bones of the infants with haemolytic disease were of normal appearance. In the two infants with rickets, aged 6 months and 11 months, the metaphyseal changes typical of the condition were seen.

Of the five infants, all premature, whose blood Wassermann and Kahn reactions were positive, the two in whom the double contour effect was seen showed no radiological evidence of any other skeletal changes. The other three showed definite bone changes suggestive of syphilis in the form of osteochondritis, osteitis, and periostitis. These lesions tended to be multiple, affecting more than one bone, and to be asymmetrical in distribution.

FIG. 1.—Radiograph showing well marked double contour effect more marked on the anterior surface of the tibia.

FIG. 2.—Enlargement of the same bone.

FIG. 1.

FIG. 2.

FIG. 3.—Marked double contour effect limited to the inner side of the tibial shaft.

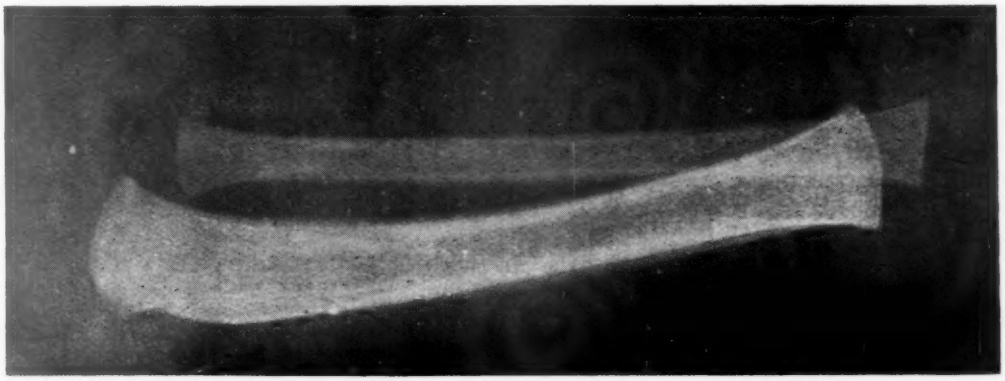

FIG. 4.—Double contour effect most marked at the lower end of the anterior tibial shaft and in the middle of the posterior surface.

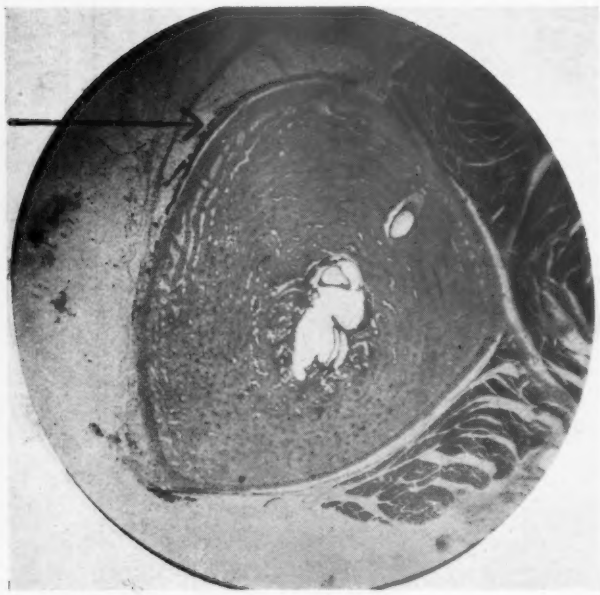

FIG. 5.—Cross section of tibia of Case 72 (low power photomicrograph). The arrow points to the Indian ink which had been injected in the region of the double contour. Note the porosity of the subadjacent bone tissue resulting from the large, arciform, primitive vascular channels.

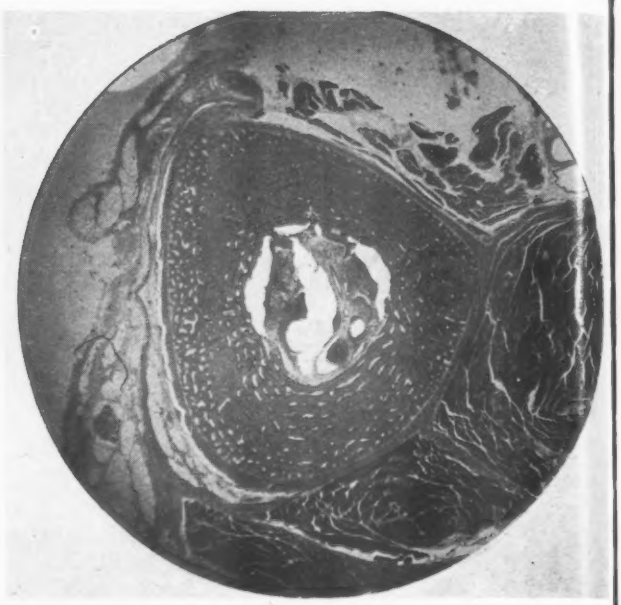

FIG. 6.—Cross section of control bone. The vascular channels are smaller and more uniformly dispersed, indicating a less concentrated apposition of bone tissue.

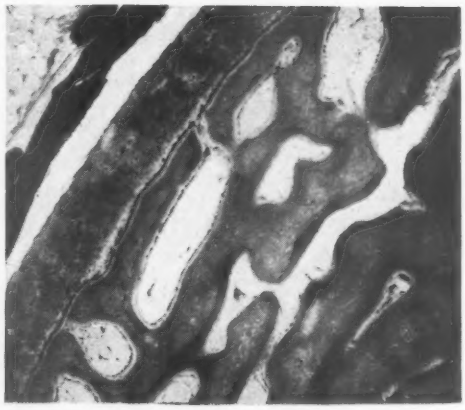

FIG. 7.—Higher power view of tibia of Case 72. The outermost portion of the bone is shown. The tissue is normal and its appearance suggests rapid deposition.

Histological Material

In order to determine the histological appearances of the bones showing the double contour effect, post-mortem material was obtained from 20 other infants who had no known skeletal abnormality. The bones were removed and radiographed from different angles to demonstrate the double contour effect if any were present. It was observed in only two cases, and in these it was not well marked. The area of the bone showing the double contour effect was ' marked ' for the histologist by inserting pins under radiographic control through the soft tissues of the limb down to the bone in the area, and then injecting Indian ink into the soft tissues round the bone at the points of the pins. The pins marked the area in the radiograph and the Indian ink identified that area to the histologist.

Histology

In the first case examined histologically the tibia and fibula were left in their natural relationship with some adherent soft tissue. After fixation and decalcification a block of tissue was excised by transverse cuts in the mid-shaft region and was embedded in paraffin wax. In the second, in which the Indian ink had been injected into the soft tissue around the bone where the double contour effect had been demonstrated radiologically, a similar block of tissue was embedded in low viscosity nitrocellulose. Control blocks were also prepared from bones which did not show the double contour effect.

The histological picture was essentially similar in both the affected cases. The bones appeared perfectly normal, except that in the region where

the double contour had been demonstrated the bone tissue was notably reticular in appearance, trabeculae of woven bone surrounding very large primitive vascular canals which were often arciform (Fig. 5). The appearance almost suggested that there might be two outer boundaries to the shaft of the bone. In one case the outermost bone was continued toward the periosteum in the form of flame-shaped tongues.

The bone tissue in the regions described appeared normal histologically, and with the technique applicable to decalcified material, there was nothing to suggest the existence of 'osteoid borders' such as would be found in rickets. Moreover, the pattern formed by the trabeculae resembled that normally encountered where bone deposition is proceeding rapidly, such as in fracture callus or during the initial stages of membrane bone formation. The tall, basophil osteoblasts surrounding the bone also suggested intense bone deposition (Fig. 7).

It would appear that in the region of the double contour effect the bone tissue is more porous than usual, and that quite large and probably more or less continuous spaces occur in its substance. Such large spaces were not seen in the control sections (Fig. 6); they would obviously absorb less radiation than the surrounding denser bone, thereby probably accounting for the thin, radiolucent line on the inner aspect of the double contour described above. The outer portion of the contour, comprising the continuous linear shadow, is in all probability cast by the outermost trabeculae consisting of the most recently deposited bone tissue. It should, however, be stressed that only tentative conclusions are justified in view of the paucity of histological material.

The rather striking configuration of the bone tissue is probably a reflection of a localized acceleration of growth. Subperiosteal accretional deposition of bone tissue cannot proceed equally and uniformly around the entire perimeter of a developing bone since the ultimate sectional outline is never perfectly circular and is usually pyriform or even triangular. Increase in thickness of the shaft must then be attained by a differential deposition rate. The site of maximum deposition may vary from time to time which would account for the disappearance and reappearance of the double contour effect should this be observed.

Discussion

Incidence. While this investigation was in progress Glaser's paper (1949) was published. It seems clear that the double contour effect which he describes is similar to that which we have studied. He investigated 100 premature infants at monthly intervals, and found the double contour effect in the ulna in 32 cases, in the radius in 27, in the tibia in 24, and in the fibula in eight. The incidence in the various bones differs from that in our series, but is more likely to be an accurate indication of the true incidence in premature infants, since it is based on much larger numbers. He noted that the effect often appeared first in one bone and later in others; that its first appearance was commonly in the third and fourth months of life, and that it tended to disappear in the seventh, or, more frequently, the eighth month. In 67 mature infants whom he investigated by a single film of each bone taken on one occasion only, he found the double contour effect in the ulna in 46, the radius in 37, the tibia in 24, and the fibula in 14, and he noted that the changes tended to disappear about two months earlier than in the premature infants.

Causation. He states that the double contour effect is produced by the x-rays falling on a bone in a certain direction relative to the bone, its crests and the film, and supports his contention by films taken of the same bone in different positions relative to the direction of the rays. We were unable, in repeated experiments both with living infants and with excised bones, to relate the double contour effect to the projection of a crest or anatomical ridge; also many of our cases showed double contour whatever the position of the bone relative to the rays. Moreover, the histological appearance in the region of the double contour is not that of a crest, but of a localized exaggeration of appositional growth process in the bone. We believe, therefore, that the effect is not produced by projection but by this local acceleration of the growth of the bone.

Davidson and Merritt (1934) noted a periosteal reaction early in rickets. Von Chiari (1938) considered rickets to be a contributory, but not the main, factor in the causation of the double contour effect. He found pyodermia to be the most frequently associated condition, but did not regard it as of prime importance. He also rejected syphilis as a cause. Malmberg (1945) also regarded the effect as an early sign of rickets, because he found a double contour in 39% of 114 premature infants who had received prophylactic vitamin D, and in 64% of 42 controls who did not receive the vitamin, and also because he observed that many infants who showed the double contour effect later developed rickets. Infants of birth weights under 1,500 g. showed the change twice as commonly as those over that weight. Glaser did not observe rickets develop in his infants showing the double contour effect. Similarly, it did not follow in our series. Moreover, such ancillary tests as were carried out in our cases

failed to show any evidence of rickets, though it must be admitted that the infants could conceivably have suffered a transient relative deficiency of vitamin D. In our opinion, therefore, the double contour effect is not caused by rickets.

Congenital syphilis is unlikely to be a cause of the double contour effect in view of the number of infants in whom the change was seen and who showed no other evidence of such infection. On the other hand, it may be impossible to differentiate radiologically between syphilitic periostitis and the double contour effect when the periostitis is not accompanied, as it usually is, by osteochondritis and osteitis. In such cases a diagnosis of syphilis should be based solely on other evidence.

A periosteal reaction in the shafts of the long bones has been described in infants suffering from hypervitaminosis A (Toomey and Morissette, 1947; Rothman and Leon, 1948). This reaction may have an irregular and fuzzy outline, or may take the form of a clearly defined periosteal line similar to the double contour effect. These bony changes have, however, been accompanied by other manifestations of hypervitaminosis such as loss of weight, progressive emaciation, haemorrhagic rhinitis, and loss of hair, and have been produced by the prolonged administration of vitamin A in doses of 100,000-250,000 units daily. The infants in this series were daily receiving 10,000 units of vitamin A, and none showed such a syndrome. It is, therefore, considered very unlikely that hypervitaminosis A plays any part in the production of the double contour effect in these infants. It must be remembered, however, that it is common practice to give what is considered to be an adequate daily amount of vitamin D in a form that includes vitamin A in quantities which may possibly be excessive for some infants. Overdosage of vitamin A must, therefore, be considered as a possible cause of a double contour effect in an infant in whom the intake of the vitamin is unknown.

Ascorbic acid was administered to these infants in adequate doses from the second week of life, and the radiological appearances of scurvy are quite unlike the double contour effect.

Infantile cortical hyperostosis is characterized radiologically by gross changes in the long bones which do not resemble the double contour effect. Moreover, the mandible and clavicles are the bones most often affected, and there are accompanying fever and constitutional disturbances.

Infants with long bones fractured during delivery have not been included in this series, but the radiological appearances in the region of fractures in other infants bore no resemblance to the double contour effect. Also there was no significant difference between the degree and location of the double contour effect in infants in this series born by breech delivery, and in those born by vertex presentation. Similarly, there is no evidence to support the view that the appearance is due to subperiosteal haematoma. In fact, the histological findings completely refute such a theory. Trauma, then, cannot be regarded as in any way responsible for the double contour effect. Similarly, there is no evidence that osteogenesis imperfecta plays any part in its production.

The double contour effect is a normal radiological finding in the long bones of some newly born infants. The cause is shown histologically to be due to a local exaggeration of the normal appositional growth of bone. The effect is visualized best and most frequently in the younger infants, particularly the premature ones. Its appearance is not related to any known type of disease, and its presence in association with other diseases must be regarded as being entirely fortuitous.

Summary

An investigation into the occurrence and cause of a double contour effect in radiographs of the long bones of infants is described. Theories of causation are discussed and evidence is submitted in favour of its being due to local exaggeration of the normal growth process.

We wish to express our thanks to Professor N. B. Capon for his helpful advice in the presentation of our findings, and to the staff of the Mill Road Maternity Hospital for their willing cooperation during the investigation.

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THE CLINICAL FEATURES, DIAGNOSIS, AND OSSEOUS LESIONS OF GARGOYLISM EXEMPLIFIED IN THREE SIBLINGS

BY

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Gargoylism (Ellis, Sheldon and Capon, 1936), lipochondrodystrophy (Washington, 1940), dysostosis multiplex or chondro-osteodystrophy, of the type described by Hurler (1917) and Hurler (1919), is a remarkable symptom-complex consisting in the main of two basic components.

The first is a defect in cartilage maturation which involves most of the bones of the body and accounts for dwarfing, kyphosis, restriction of joint movement, crouching posture, and claw-like hands. Depression of the nasal bridge, hypertelorism, prominent supra-orbital ridges, and prognathism partly explain the ugliness.

Secondly, the storage of an abnormal macromolecular substance of uncertain type occurs not only in reticulo-endothelial cells, but in parenchymatous and connective tissues all over the body. This produces hepato-splenomegaly, cardiac enlargement and failure, mental deficiency (Reilly and Lindsay, 1948) corneal clouding (Rochat, 1942), pyramidal tract involvement (Jervis, 1950), and deafness. Thickened, coarse, pasty skin, thick lips, large ears, and a large protruding tongue complete the gargoylistic appearance.

The hypertrichosis and frequent severe chronic nasal infection (Lindsay, 1950) are not obviously explicable.

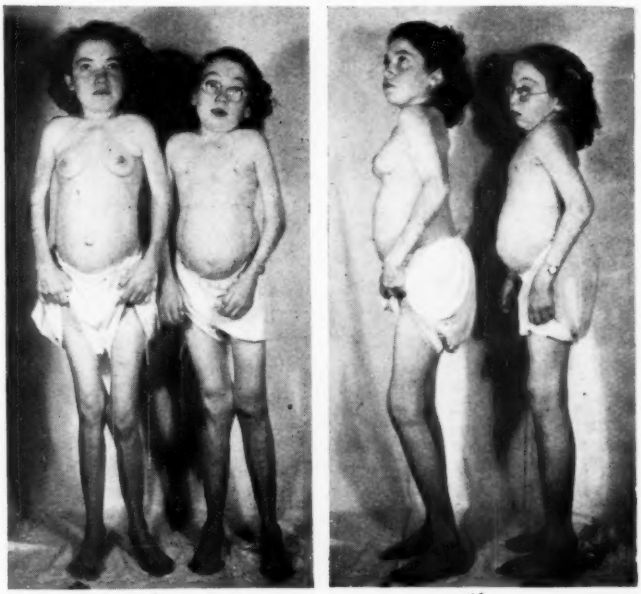
The condition is an inherited one, starting in early childhood. It appears to be caused by a monomeric autosomal recessive gene and, like the Laurence-Moon-Biedl syndrome, the Ellis-van Creveld syndrome, and a few others, provides an excellent example of the potentiality of a single gene to produce multiple effects which are not necessarily morphologically connected.

Not every gargoyle shows all the features mentioned above and any one or more of the various outstanding peculiarities may be missing in individual cases (Jervis, 1950). On the other hand, it seems reasonable to say that the diagnosis cannot be made unless there is clinical evidence of both the fundamental defects, chondro-osseous and 'storage,' or either with a family history.

By far the most important cause of death is cardiac failure. Lindsay found that out of 19 fatal reported cases, 14 died in this way. The present family came under our observation when the elder affected sister entered Groote Schuur Hospital with severe congestive cardiac failure.

Case Reports

Case 1. In Daphne (Fig. 1), a white girl aged 20, deformities had been observed when she was 3 years old. The neck seemed short, the trunk small, the fingers stiff

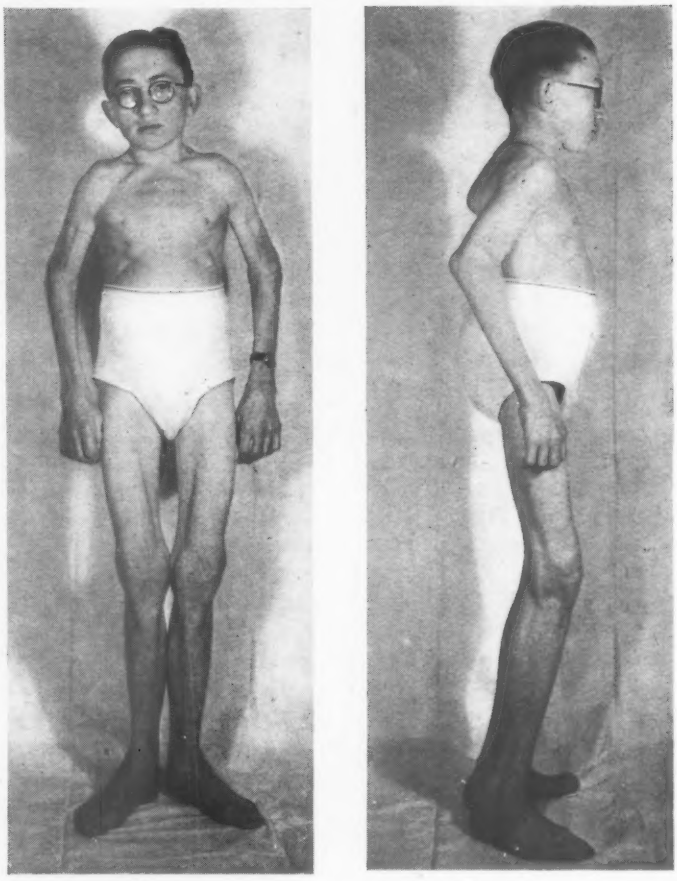


1a. 1b.

FIG. 1.—Daphne and Patricia. Note facies, abdominal protrusion, hirsutes, genu valgum, short trunk.

and flexed. She never remembers having a full range of movement at any limb joint. In December, 1949, she had pneumonia, and since then suffered from increasing breathlessness on effort. During the month before admission her feet swelled, she developed dyspnoea at rest, and became extremely ill.

She entered hospital in September, 1950, in congestive heart failure, with cyanosis, distended neck veins, sacral and pedal oedema. The liver was tender as well as being much enlarged. Tachycardia (regular, sinus rhythm, 144) was present with a normal blood pressure of 120/90. The apex beat was beyond the mid-clavicular line. There was gallop rhythm and accentuation of the second pulmonic sound. When the heart slowed a marked rumbling systolic murmur, maximal at the apex, was heard.



2a. 2b.

FIG. 2.—Dudley. Note facies, winged scapula, long limbs, large elbow joints (2b), thin thighs. The maximum abduction at the shoulders (2a) and extension at the elbow (2b) is shown.

A chest radiograph showed general enlargement of the heart with a straightening and even bulging in the region of the conus on the left, and congestion in the lungs (Fig. 4). An electrocardiogram employing 17 leads showed (Fig. 4a) a tall biphasic P in lead 1, 2, V1 and V2 (left auricular hypertrophy), right ventricular hypertrophy and clockwise rotation. Any effects due to myocardial damage were masked by digitalis.

The heart responded well to digitalis and bed rest with a slowing of the pulse, diuresis, lessening of cyanosis and of breathlessness. She was able to walk out of hospital three weeks after admission.

As far as other features of the case were concerned, the girl was mentally normal and was a trained shorthand typist. She was under 5 ft. in height.

The head was normal in size and shape and her face, except for the cyanosis, not unpleasing. The hair was dark and abundant, the eyebrows were thick, and the forearms covered with long black hair. The neck and trunk were short, and the muscular development poor. The wrists were large, and all movements of the limbs and spine were limited. There was spindle swelling at the phalangeal joints and the fingers could not be extended, so that the hands were grotesque and claw-like (Fig. 3). The abdomen was protuberant with an umbilical hernia.

Both liver and spleen were enlarged down to the navel and were smooth and firm. There was palmar erythema. Further evidence of defective liver function after the cardiac failure had subsided was the plasma protein ratio (albumin 3·2: globulin 3·8) the abnormal glucose tolerance curve, and poor hippuric acid excretion after an intravenous injection of sodium benzoate; the flocculation tests were normal. Renal function was satisfactory as judged by urine concentration, blood urea (31 mg. per 100 ml.), urea clearance, and the phenol red test.

The corneae were diffusely hazy but the condition was so far mild, and no discrete opacities could be seen with a slit lamp.

The central nervous system was normal.

Case 2. Dudley, aged 22, a brother of Daphne, was a trained accountant. A haziness of the eyes was noticed when he was 3 years old. He had complained of aching pain in the lower back in recent months.

He was certainly ugly, but without the typical facies of gargoylism (Fig. 2). He had a worried looking, young-old face with dry, pasty skin, gross myopia, peaked nose, receding chin, and prominent ears. His eyebrows and hair were thick, but there was no facial hair (he shaved once a month as a token), no axillary hair, and the pubic hair was scanty and flat-topped. The corneae were very cloudy.

He had palmar erythema, cyanosed hands and feet, mottled forearms, and superficial telangiectases on the feet. His teeth were good, but the lower incisors bit outside the top ones.

The upper abdomen was protuberant, with an umbilical hernia, and firmly enlarged liver but no splenomegaly.

FIG. 3.

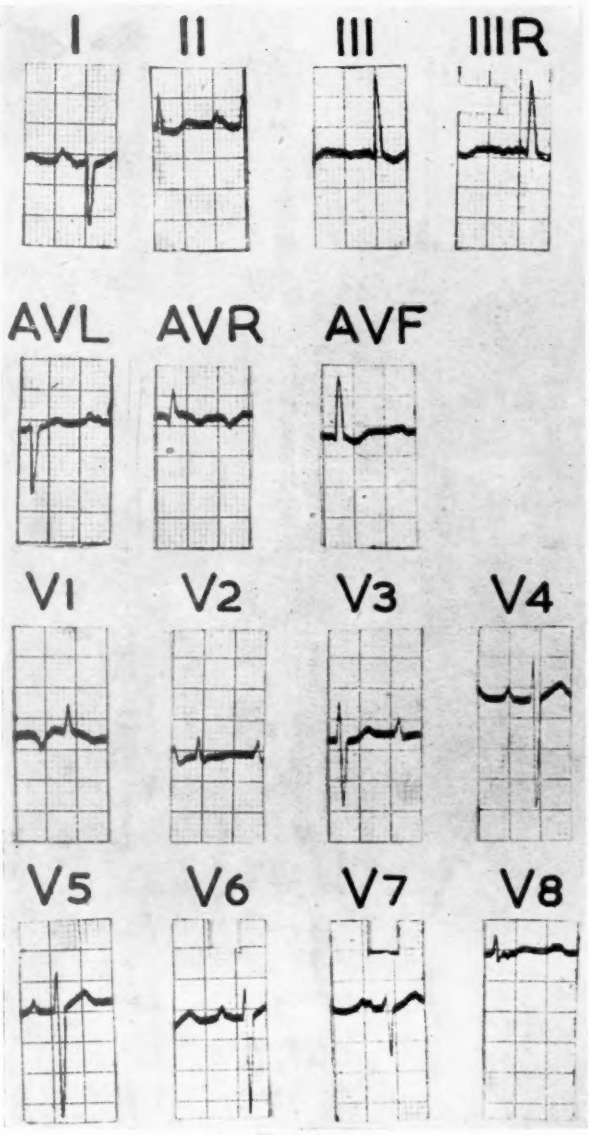


FIG. 4a.

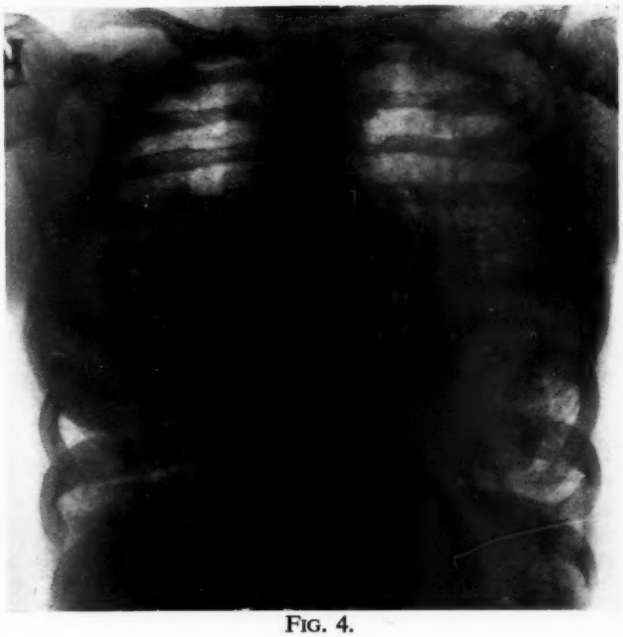


FIG. 4.

FIG. 3.—Hand from each sibling showing maximum extension of fingers and enlargement of phalangeal joints.

FIG. 4.—Daphne. Enlarged heart with straightened left border. Congested lung fields. Wide horizontal lower ribs and short clavicles.

FIG. 4a.—The electrocardiogram after the administration of digitalis, shows evidence of left auricular hypertrophy, right ventricular hypertrophy, and clockwise rotation. It is impossible to say whether actual myocardial damage is present owing to the effect of digitalis.

FIG. 5a.

FIG. 5c.

FIGS. 5a, b, c.—Shoulder girdles to show short, deformed clavicles, expanded medially and deficient laterally; irregular and enlarged humeral epiphyses; poorly formed glenoid fossae.

FIG. 5b.

FIG. 9.

FIG. 9.—Knee joint in Morquio's disease showing, as distinct from gargoylism, wide joint spaces and metaphyseal expansion.

FIG. 6.—Radiograph of Patricia's chest to show wide, horizontal ribs with narrow necks.

7a.

7b.

FIGS. 7a, b, c.—Radiographs of hips and pelves showing enlarged femoral heads, flattened in b and c, and grossly deformed brim in c.

7c.

He was 5 ft. tall with a short trunk and bony, thin legs, the thighs leaving a gap inside his pants (Fig. 2). He had thoracic kyphosis, slight scoliosis, winged scapulae, sharply angulated clavicles, genu valgum, irregular enlargement of the knee joints, the malleoli and the calcanea, flat feet, and overlapping calloused toes. Movement of the spine, hips, knees, shoulders, elbows, and wrists was limited. In particular, abduction at the shoulder was absent (Fig. 2a). The elbows were large, pointed, and permanently flexed (Fig. 2b), the fingers knobbly and claw-like (Fig. 3).

There was a rumbling systolic murmur all over the precordium but no other signs in the heart.

The testicles seemed normal.

Gait was waddling.

Heredity

There are three affected siblings of both sexes in the family, with three normals (one died at an early age), and no other member is said to suffer from the condition. The parents are not related. Autosomal recessive inheritance would explain this familial incidence, as in other reported families, despite the high proportion of affected members in the present generation.

Radiological Features

The radiological findings in these three patients are so similar that they may be considered together. The skulls are virtually normal, except that the maxillae protrude and the chin recedes. Dolichocephaly, syncephaly, frontal bossing, and elongated sella are not seen. The vertebrae show only mild changes; irregularity in the anterior, superior, and inferior surfaces, slight flattening and diminution of disc space, but no wedging or lipping. These changes are mainly in the thoracic region.

FIG. 8.—Patricia. Abnormally shaped metacarpal shafts with metacarpophalangeal joint expansion. Tapering terminal phalanges. Radial epiphyses face inwards.

Case 3. Patricia, aged 18, a sister of Daphne and Dudley, is at a special school for the mentally backward. She gets frequent nasal catarrh.

Her appearance was more typically gargoylistic than that of her siblings (Fig. 1). The face was ugly and round, the mouth open and the large fissured tongue visible, the chin flabby and very receding, the skin thick, coarse and pale, the ear lobes large. She was very short-sighted, and the corneae were severely clouded. The bridge of the nose was flat, the supraorbital ridges heavy and topped by a receding forehead. The hair of the head was normal, of the axillae and pubis absent, of the forearms excessive and black. There was no breast development and no neck. The feet were cold and a little cyanotic. The liver was enlarged in to the pelvis, the spleen one hand's breadth below the costal margin. The abdomen protruded, and a hernia had been repaired. There was a softish systolic murmur all over the precordium and the pulmonary second sound was accentuated.

The skeletal system was similar to that of Dudley, without such great limitation of movement.

The clavicles are irregular and short with a sharp central backward angulation. They are expanded at the sternal end, but deficient laterally so that they do not reach the acromion process (Figs. 4 and 5). This lateral clavicular deficiency has not been previously commented upon in gargoylism, although it is depicted in the radiographs of other authors, for example Jervis (1950). Such a finding is reminiscent of cleidocranial dysostosis, osteodental dysplasia (Jackson, 1951a), with which condition gargoylism has no further points of comparison.

The scapulae seem short and thick and the superior portions abnormally shaped (Fig. 5). The

ribs run horizontally and their posterior parts are wide (Fig. 6). The lower ones are lanceolate, their necks thin. The pelves are ill-formed and asymmetrical; the pubic rami do not properly connect; there is acetabular irregularity and protrusion (Fig. 7).

The long bones in general show almost normal shafts, but a variable degree of irregularity of epiphyseal ossification with flattening and enlargement of bone ends (Figs. 5 and 7). The joint spaces are not widened as is the case in Morquio's disease. A thick shaft tapering towards its ends is described by Reilly and Lindsay (1948) as typical of gargoylism. This is seen in a minor degree in our cases, in which terminal bony enlargement is due mainly to the epiphyseal irregularity (Fig. 5) in contradistinction to the metaphyseal expansion in Morquio's disease (Fig. 9). The articular surfaces of the lower end of the radii face inwards. The terminal phalanges show as remarkable thin pointed talons (Fig. 8).

There is some general osteoporosis.

The Bony Defects in Gargoylism Distinguished from Morquio's Disease

From the point of view of bone structure gargoylism is classed as a general defect in cartilage maturation, epiphysis and diaphysis, affecting the whole bone (Jackson, 1951b). However, the frequent occurrence of acrocephaly, irregular skull vault, deformed mandible (hyperobtuse angle) and clavicle indicate defects in membrane bone also.

It is said that Morquio's chondro-osteodystrophy is so similar to the osseous syndrome of gargoylism that both may represent the same condition (Reilly and Lindsay, 1948; Jervis, 1950). Despite the similarities in epiphyseal and vertebral defects there are so many constant distinctions between the two diseases, apart from all the systemic effects of gargoylism, that they must be kept separate. The membrane bone abnormalities do not occur in Morquio's disease, in which the spine is always the most severely affected part of the skeletal system, and may even be the only part. Anterior central prolongation of the thoracic and lumbar vertebrae with marked platyspondyly is characteristic of severe Morquio's affection, but is not seen in gargoylism. Beyond some depression of the nasal bridge, the skull is normal in Morquio's disease. In mild cases the spine alone, or spine and hips with or without the knees and shoulders, are affected (Brailsford, 1945). The accent may be quite different in gargoylism, as in the present family. In more severe cases there is gross pigeon-chest deformity which is not exhibited by gargoyles. The wide, horizontal, ribbon-like lower ribs are typical of gargoylism, but may appear in lesser degree in Morquio's syndrome. As regards the long bones, there are several apparently inviolate distinctions. Most striking is the increased joint space in Morquio's disease (Fig. 9) without restriction of movement. The epiphyses are more irregular, fragmented, enlarged, and fuzzy in severe cases of Morquio's disease, but not flattened as in some gargoyles (Fig. 7). Reilly and Lindsay point out that the enlargement and flaring out at the ends of long bones are solely epiphyseal in gargoylism, but largely metaphyseal in Morquio's syndrome.

These distinctions, sufficient to separate skeletal gargoylism from Morquio's disease, do not necessarily mean that the two conditions are entirely unconnected. Gates (1946) has suggested a genetic connexion between the various osseous dystrophies which would explain the appearance of irregular and intermediate forms (Ruggles, 1931; Snoke, 1933; Jackson, 1951b).

The Liver and the 'Storage Substance'

Hepatic function tests are nearly always normal in gargoylism, but Daphne had a reversed albumin: globulin ratio (3·2:3·8). The blood sugar figures after the administration of 50 g. glucose were:

Fasting ..	97	mg.	per	100	ml. (Hagedorn
½ hour	114	,,	,,	,,	and Jensen,
1 hour ..	159	,,	,,	,,	capillary
1½ hours	186	,,	,,	,,	blood)
2 hours ..	152	,,	,,	,,	
2½ hours	152	,,	,,	,,	

The intravenous hippuric acid test was also defective, an amount equivalent to 0·38 g. Na benzoate being found in the urine, which is about half the lowest permissible normal.

A liver biopsy (Fig. 10) was performed after the congestive cardiac failure cleared up. Prof. J. G. Thomson reported:

> 'Histologically the liver cells are swollen, mainly due to a high glycogen content, but partly due to small droplets of fat, which show no double refraction with the polarizing microscope. The two constituents adequately explain the size of the cells; the glycogen is in excess for an ordinary liver, but not abnormal in distribution or staining reactions.'

Staining methods used were Best's glycogen stain with alcohol fixation, Sudan III with a frozen section, and haematoxylin and eosin on a paraffin section.

The 'Incomplete Syndromes'

Few, if any, gargoyles show all the reported characteristic signs of the disease, so that a definition of the 'complete syndrome' is largely conventional and dependent upon those features which were described first and those which are most outstanding.

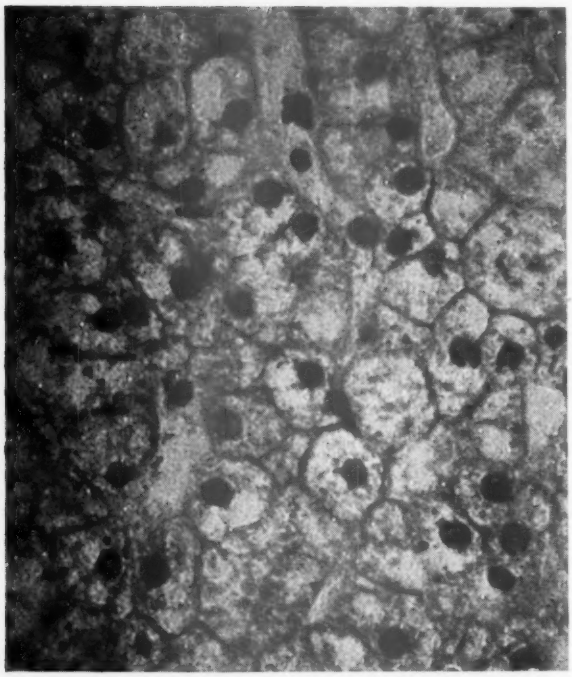


FIG. 10.—Liver biopsy, Case 1. Paraffin section stained with haematoxylin and eosin × 500. The rounded, empty-looking cells contain an excess of glycogen.

Here in one family where the diagnosis is beyond cavil two affected members are mentally normal or above normal, one is facially normal, and none show the expected vertebral lesions. Jervis (1950) considers in greater detail the 'incomplete forms' of the disease. The only essential criterion for the diagnosis seems to be the appearance together of a chondro-osteodystrophy, with features described above, and evidence of likely abnormal storage such as corneal clouding, mental defect, cardiac failure, and hepatosplenomegaly, or either with a positive family history. Patricia had at different times been treated for 'cretinism' and 'Perthe's disease of the hip,' errors which could never occur if a full history had been taken and a full examination made.

Summary

Three siblings suffering from gargoylism are described. The elder sister was admitted to hospital with congestive cardiac failure, the most important cause of death in this condition. This girl did not have the typical facies, so that 'gargoylism' in her case is strictly a misnomer. The findings in the three siblings are summarized in Table 1.

The radiological features of these cases are described, and the differentiation from Morquio's disease is discussed. It is concluded that the two conditions are quite distinct.

TABLE 1

CLINICAL FINDINGS IN THREE SIBLINGS

Sex	M	F	F
Age	22	20	17
Affected sibs	+	+	+
Parental consanguinity	—	—	—
Mental defect	—	—	+
Facies	±	—	+
Dwarfing	+	+	+
Bones: Skull	—	—	—
Bones: Spine ..	±	±	±
Bones: Ribs ..	+	+	+
Bones: Limbs	+	+	+
Hepatosplenomegaly ..	+ (no spleen felt)	+	+
Corneal clouding ..	+	+	+
Cardiac disease ..	probable	+	probable

Finally the 'incomplete' pictures or *formes frustes* of gargoylism are considered, and it is suggested that all that is needed for the diagnosis of gargoylism is the co-existence of specific osseous lesions with evidence of abnormal storage such as mental defect, corneal clouding, or hepatosplenomegaly.

Despite the fact that the term 'gargoylism' is not a good title for the disease, picking out as it does one particular feature which is not necessarily present, no better one can at present be suggested, except possibly the eponymous Hunter-Hurler's disease. Since it has now been denied that the storage substance is lipoid in nature the term 'lipochondrodystrophy' must be held in abeyance.

I am pleased to thank Professor F. Forman for his advice and Dr. H. Myers for much of the work in preparing this paper. For the histological report I am indebted to Professor J. G. Thomson, and for the photomicrograph to Mr. H. Hall, of the Physiology Department. Dr. V. Schrire was kind enough to comment on the electrocardiograph. For the radiograph and photographs I am indebted to the Radiological Department of Groote Schuur Hospital and to Mr. G. McManus and Mr. C. C. Goosen of the Department of Surgery.

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Addendum

Since this article was submitted for publication the first patient (Daphne) has died from congestive cardiac failure. She developed a diastolic murmur suggestive of mitral disease before death, which did not occur in hospital. Necropsy was refused.

The other sister (Patricia) has been ill with cardiac failure, but has not been in hospital.

Another case of gargoylism (unrelated to this family) has been discovered in Cape Town and reported in the *South African Medical Journal* by McDonald and Opie (1951), *S. Afr. med. J.*, **25,** 725.

THE VOLUME AND ACIDITY OF THE GASTRIC CONTENTS IN THE UNFED NEWBORN INFANT

BY

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The acidity of the gastric contents in the unfed newborn infant was first investigated by Szydlowski (1892a and b). He recorded the presence of free hydrochloric acid. Hess (1913) found free hydrochloric acid in varying amounts in 54 out of 55 infants, and recorded unexpectedly high values. Pollitzer (1921) made similar observations on 100 infants.

The *p*H of the gastric contents was estimated first by Tangl (1906) whose observations ranged from 1·3 to 1·8. Griswold and Shohl (1925) recorded a *p*H range of 1·7 to 4·4. Ritter (1941) found the *p*H varied from 1·3 to 4·6, and noted the absence of free hydrochloric acid in four out of 36 infants. Miller (1941) also observed the occurrence of achlorhydria and stated that the incidence of achlorhydria diminished with increasing birth weight.

No worker has as yet submitted his observations on achlorhydria and the volume of the free hydrochloric acid in relation to birth weight to a proper statistical test. For this reason it was thought desirable to undertake a new investigation into the incidence of achlorhydria and the free acidity in the newborn.

Method

The observations were made on healthy normal singleton infants of both sexes. The birth weights ranged from over 4½ lb. to 10½ lb. A sterile dry catheter was passed into the stomach and suction was applied with a sterile record syringe. When gastric contents were obtained they were transferred to a sterile, dry test tube. The material obtained was in some cases analysed immediately, but when this was not convenient the test tubes were placed in a refrigerator. Those specimens which were contaminated, e.g. by liquor amnii, were rejected.

The volume of the specimens was recorded. The *p*H was determined by the B.D.H. capillator method.

To determine the presence of free hydrochloric acid Gunzberg's test was performed. A uniform volume, 0·5 ml., was measured into a watch glass. This was placed on a white surface and titrated with N/10 NaOH from a microburette graduated in hundredths of a millilitre. On five occasions, owing to the small volume of the specimen, 0·3 ml. was used for titration. Deferring to long established custom Topfer's reagent was used as an indicator, though it was recognized that thymol blue would have given a more accurate end-point in estimating the acidity.

Results

Birth Weight. The infants were arranged in the order of their birth weights and grouped in half-pound unit intervals, the lowest weight interval being over 4½ lb. to 5 lb. inclusive (Fig. 1). The birth weight distribution shown is not representative of the newborn infant, because an effort was made to collect specimens more frequently in the higher and lower birth weight groups. The mean weight of the 154 infants was 7·43 lb., and the standard deviation 1·28 lb.

Volume of the Specimens. The measured volumes of the specimens are plotted against the birth weights in Fig. 1. The mean volume for each birth weight group is also shown. The correlation coefficient is +0·074, and the mean volume of all the specimens is 2·65 ml. with a standard deviation of 2·05 ml.

***p*H.** In a similar manner the *p*H is recorded in Fig. 2. The correlation coefficient is +0·050, and the mean *p*H of all specimens is 2·52 with a standard deviation of 1·53. A *p*H of more than 2·8, the end-point for free hydrochloric acid, was observed in 43 instances (27·9%). In four of these instances the *p*H was 3·0 and the Gunzberg test was positive. The mean *p*H for each weight group is also shown.

Achlorhydria. The incidence of achlorhydria is shown in Fig. 3.

Free Acidity. The volume of the free acidity which was found to be present in 115 infants is shown in Fig. 4. The mean weight of these infants is 7·36 lb. with a standard deviation of 1·24 lb.

The mean volume of all the observations of the volume of the free acidity is the equivalent of 21·44 ml. N/10 H.Cl per 100 ml. of gastric contents with a standard deviation of 11·89 ml. The correlation coefficient is −0·096. The mean volume of the free acidity in each birth weight group is also shown.

The volumes of these specimens are plotted against the free acidity expressed as the equivalent of N/10 H.Cl per 100 ml. of gastric contents (Fig. 5). The correlation coefficient is +0·098. The mean volume of the specimens is 2·87 ml. and the standard deviation is 2·06 ml.

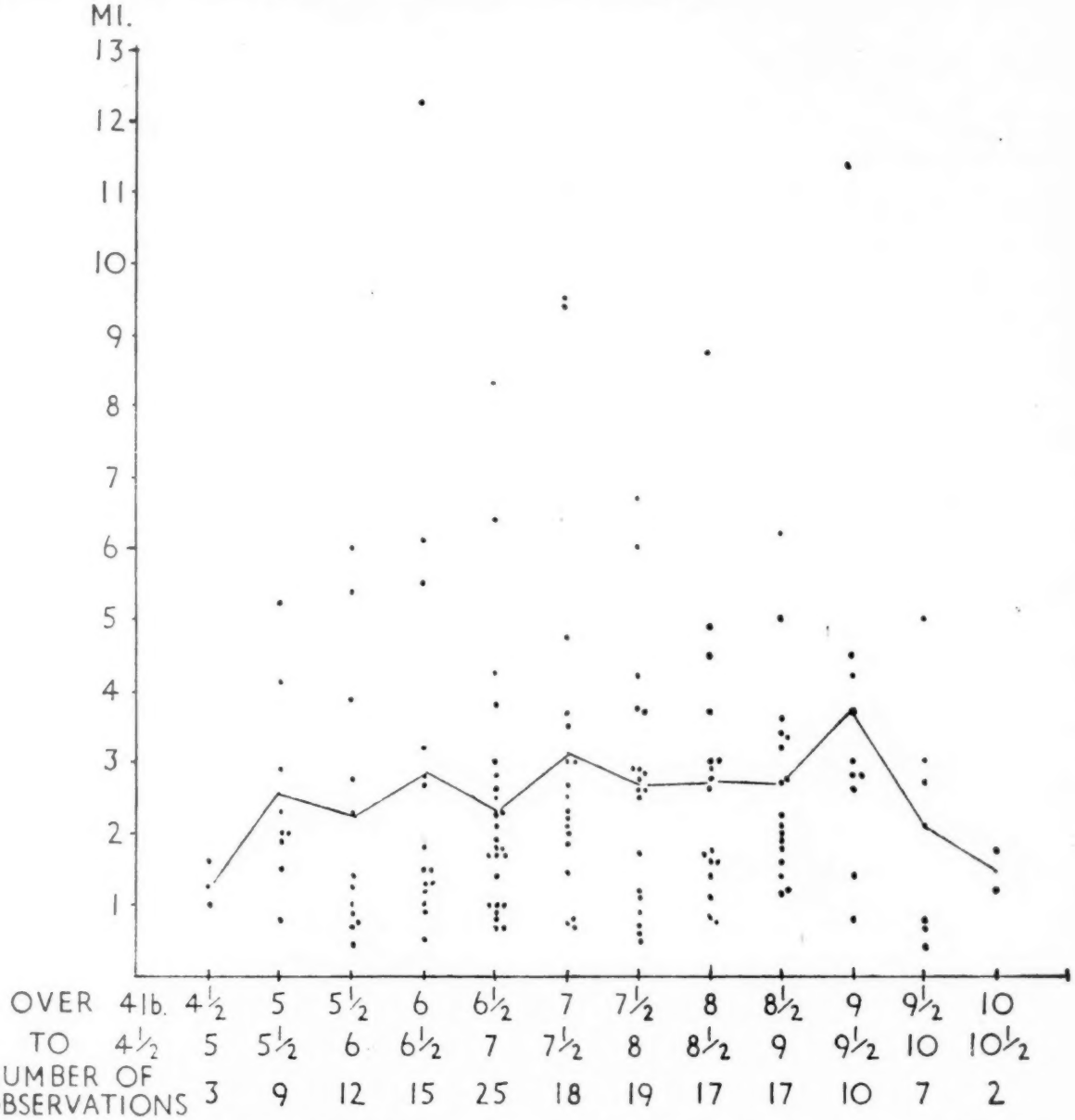

FIG. 1.—The volume of the gastric contents recovered from the unfed newborn infant in relation to the birth weight.

Discussion

The volume of the gastric contents in the unfed newborn infant has seldom been recorded. In a series of 15 infants ranging in weight from 4 lb. 9 oz. to 9 lb. 1 oz. Gellis, White, and Pfeffer (1949) found the average quantity to be 2 ml. They measured the volume to the nearest millilitre, and in one-third

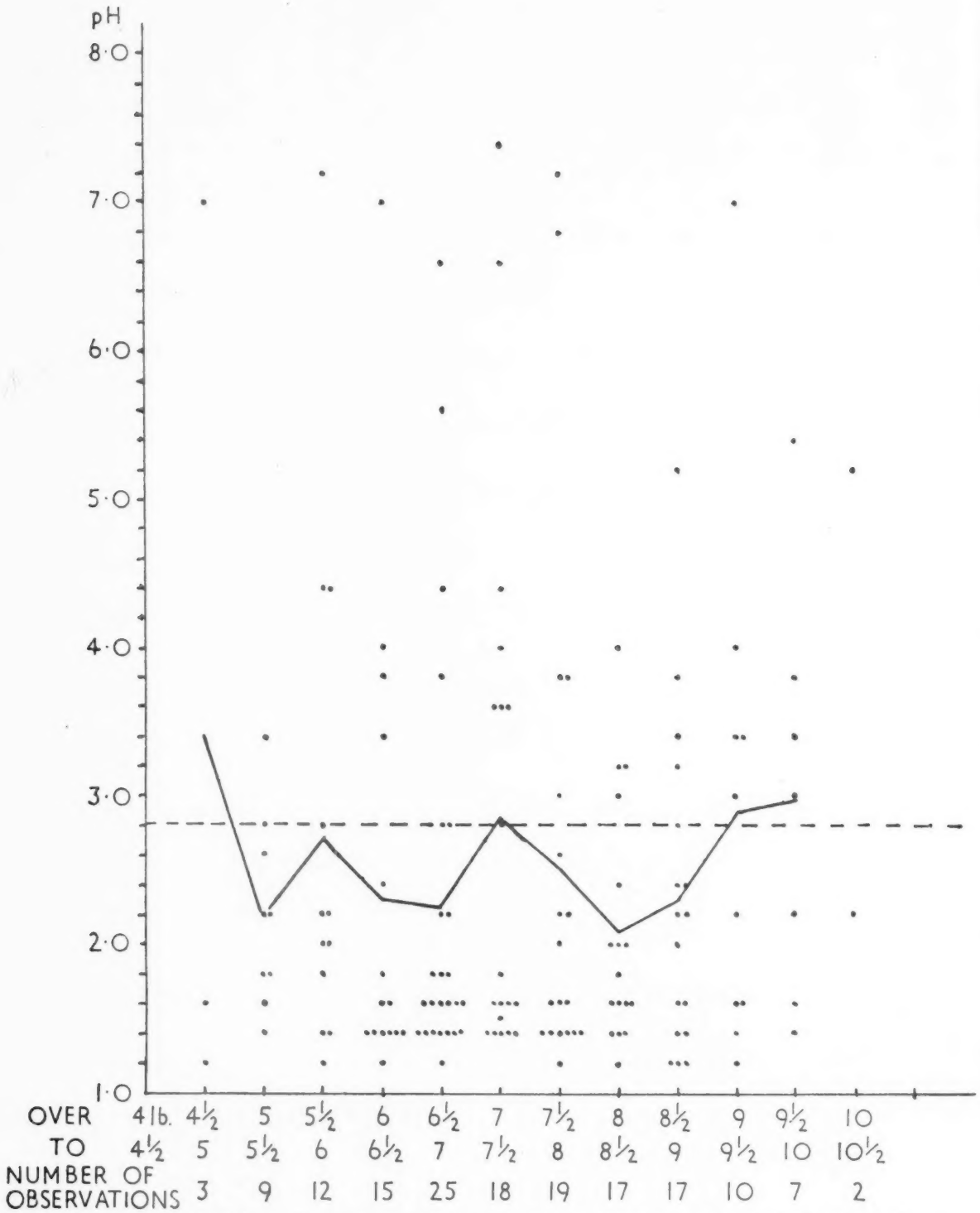

FIG. 2.—The *p*H of the gastric contents of the unfed newborn infant in relation to the birth weight.

of their infants no specimen was obtained. When these five cases are omitted the mean volume becomes 3·15 ml. Miller (1939) measured the volume to a tenth of a millilitre. In 93 normal infants, who were within the same weight range as the infants of the present investigation, the mean volume was 2·46 ml. These figures are close to the mean of 2·65 ml. now reported.

The range of the volume of the gastric contents reported by Gellis *et al.* (1949) was from 1 ml. to 7 ml. The range of the volume of the 93 specimens measured by Miller (1939) was from 0·1 ml. to 10 ml. In the present investigation the volume ranges from 0·4 ml. to 12·25 ml., and the most frequent measurement was 3 ml. This measurement occurred in 4·55% of the 154 cases.

The lack of relationship between the birth weight and the volume of the gastric contents is shown in Fig. 1, and statistical confirmation is obtained from the correlation coefficient of +0·074.

In this series of observations the *p*H ranged from 1·2 to 7·4, and is greater than that reported by Tangl (1906), Griswold and Shohl (1925), and Ritter (1941).

It is agreed that free hydrochloric acid is present if the *p*H is 2·8 or less. This level is indicated in Fig. 2. All the specimens on or below the 2·8 line were Gunzberg positive. In addition four specimens with a *p*H reading of 3·0 were Gunzberg positive. This apparent contradiction is readily accounted for by the element of personal error which enters into all experimental observations. It occurs the more easily in micro-estimations. Thus 39 of the 154 specimens showed achlorhydria, i.e. 25·3%. This figure is practically identical with the 26·5% incidence of achlorhydria in a birth weight range from over 4 lb. 8 oz. to 9 lb. 8 oz. inclusive, calculated from Miller (1941).

Examination of Fig. 2 will show that the *p*H observations are widely scattered and do not suggest

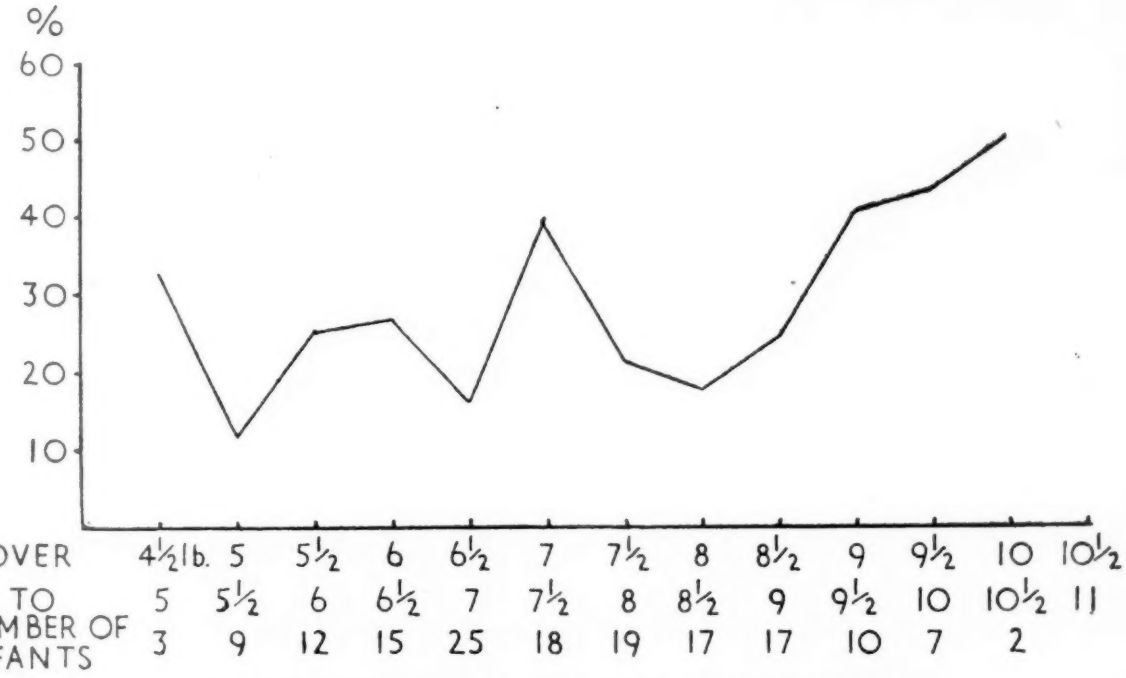

FIG. 3.—The percentage of unfed newborn infants with achlorhydria.

any relationship to birth weight. The correlation coefficient, +0·050, is not a significant one.

Inspection of Fig. 3 suggests that there is no relationship between the birth weight and the incidence of achlorhydria. This finding has its counterpart in Fig. 4 which fails to disclose a relationship between the birth weight and the volume of the free acidity, the correlation coefficient for which is −0·096, and is not statistically significant.

These findings are contradictory to those reported by Miller (1939, 1941). This can be explained partly by the different arrangement which Miller adopted for his data, and partly by a difference in the source from which Miller obtained his data. Miller's data are arranged in birth weight groups of four unequal

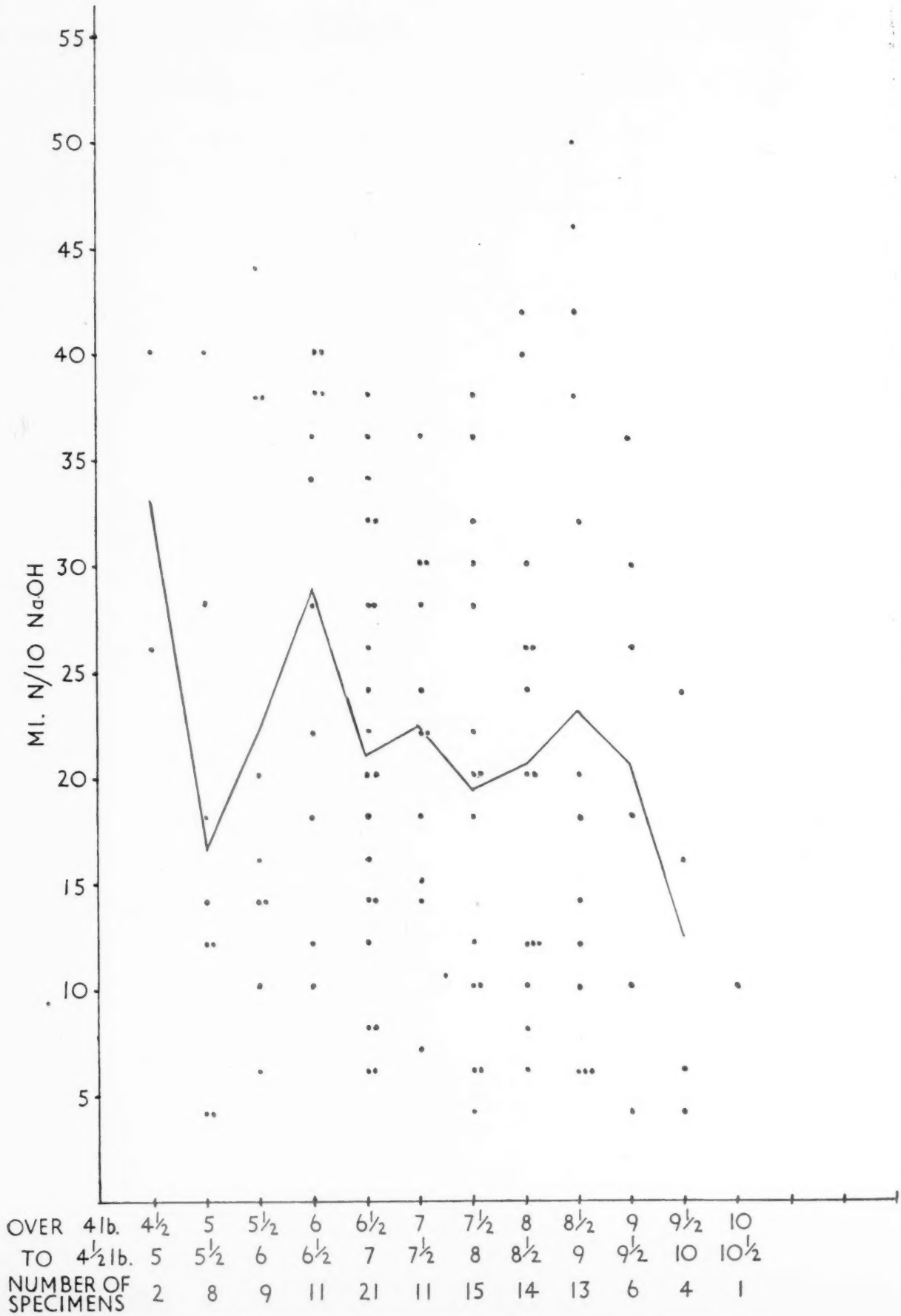

FIG. 4.—The free acidity in the unfed newborn infant in relation to the birth weight.

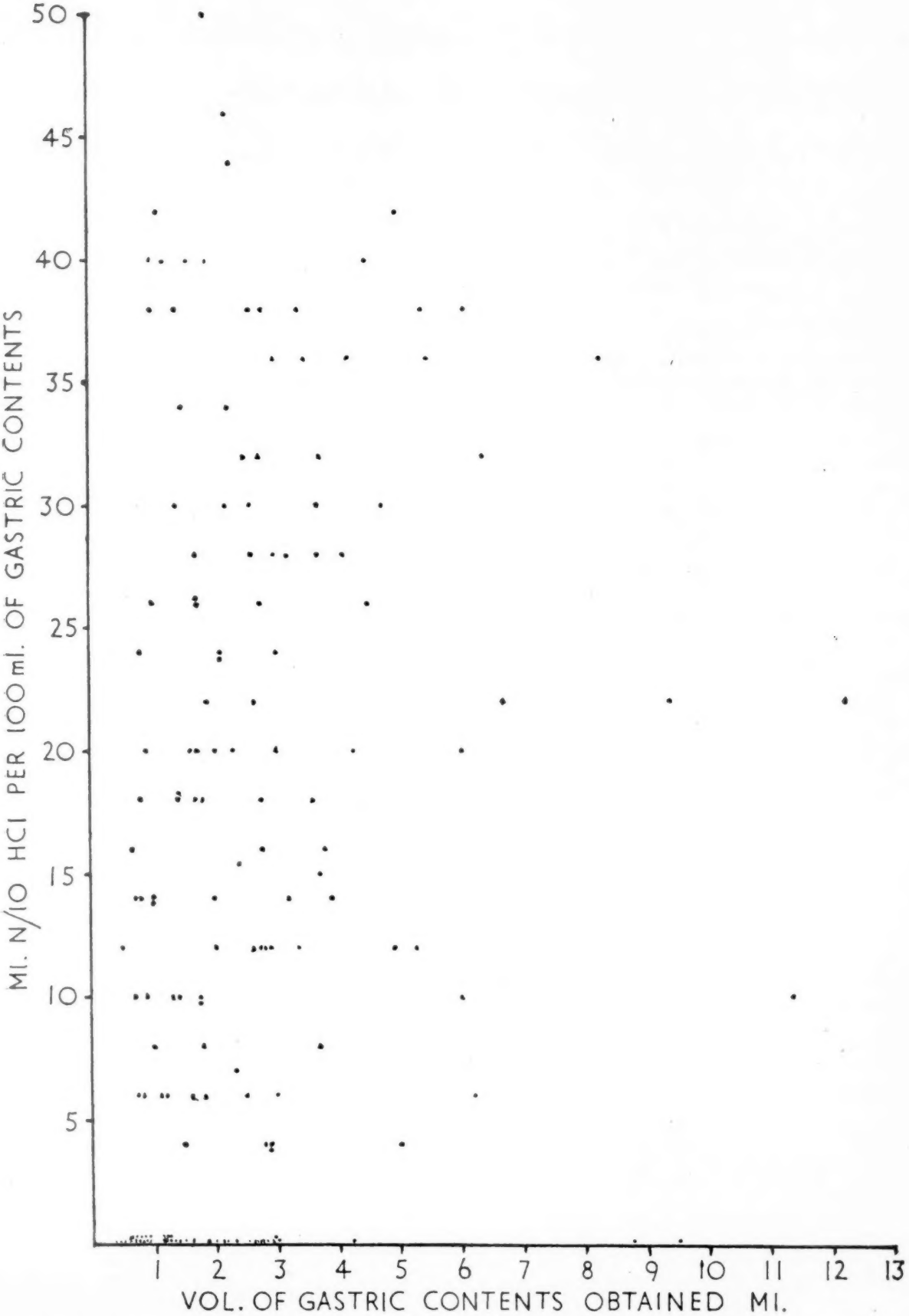

FIG. 5.—The free acidity and the volume of 115 specimens of gastric contents from unfed newborn infants.

TABLE 1

FREE ACIDITY IN 3–3½ LB. BIRTH WEIGHT GROUP

	Birth Weight	Volume of Gastric Contents (ml.)	Gunzberg Reaction	*p*H	Free Acidity (ml. N/10 H.Cl per 100 ml.)
Male ..	3 lb. 5 oz.	0·6	+	2·2	8
Female ..	3 lb. 8 oz.	1·7	+	1·4	36

ranges of weight, while of the observations made on infants weighing 5½ lb. or less at birth, at least 26% were made on twins. There is only one observation made on a singleton weighing less than 4 lb. at birth and it showed an absence of free acidity.

During the present study two singleton infants in the birth weight group over 3 lb. to 3½ lb. inclusive were examined (Table 1). It is of interest to note that both showed the presence of free hydrochloric acid.

It is also shown in this investigation that there is no relationship between the volume of the specimen and the amount of the free acidity (Fig. 5). The correlation coefficient of +0·098 is not significant.

If there were any relationship between the birth weight and the volume of the free acidity at birth or the existence of achlorhydria at that time, it would be reasonable to expect similar results in each of a set of twins. The results obtained from an investigation of seven sets of twins are shown in Table 2. It will be seen that sets Nos. 1 and 2, which by any test are the smallest and most immature, show similar amounts of free acidity in each of the twins in each set. In set No. 3 which is more mature, there is a difference of 1 lb. 7 oz. between the twins who are presumably of the same period of gestation, and the bigger of the twins shows a free acidity of less than half that of the smaller. Both twins of set No. 4 are achlorhydric though this is a more mature set than either set Nos. 1 and 2. It should also be noted that there is a difference of 2 lb. 1 oz. between the birth weights of the twins of set No. 4. In sets Nos. 5 and 6, one twin in each set is achlorhydric. In one case it is the larger twin, and in the other the smaller one which is achlorhydric. Both these sets of twins are more mature than sets Nos. 1 and 2. In set No. 7 no specimen was obtained from one twin while the other was achlorhydric. These data do not lend support to the view that there is a relationship between birth weight on the one hand and the presence of achlorhydria or the volume of free acidity on the other.

It is unfortunate that a comparison cannot be made with the observations on twins by Miller (1939), because the sets of twins in Miller's publication cannot be identified with certainty.

It has been suggested that some gastrogenic

TABLE 2

VOLUME, *p*H, AND FREE ACIDITY OF GASTRIC CONTENTS IN SEVEN SETS OF TWINS

	Birth Weight				Duration of Pregnancy	Vol. of Gastric Content		*p*H		Free Acidity (ml. N/10 H.Cl per 100 ml.)	
Twin No.	1		2			1	2	1	2	1	2
Set No.	lb.	oz.	lb.	oz.		ml.	ml.				
1	3	8½	3	8	?	0·7	0·6	1·6	1·6	32	34
2	4	9½	3	13¾	34 weeks	0·77	1·3	1·4	1·4	34	30
3	6	0	7	7	38 weeks	1·3	1·6	1·6	2·4	28	12
4	4	0	6	1	36 weeks	0·65	1·35	7·35	7·0	—	—
5	5	4	4	6½	37 weeks	2·1	0·8	1·8	5·0	14	—
6	5	14	5	10	38 weeks	0·7	3·2	6·0	1·6	—	36
7	5	6	5	7½	37 weeks	1·1	Nil	6·0	Nil	—	Nil

hormone is supplied to the infant *in utero* either from the mother or the placenta. While these observations on twins do not support this suggestion, since dissimilar results are obtained in each of a set of twins, some consideration must be given to the possibility that one twin of a set may be more able to utilize such a hormone than the other twin, or may receive a greater quantity of hormone.

Summary

The acidity of the gastric contents of the unfed newborn infant has been investigated in 154 singleton infants and in seven sets of twins.

The birth weight range of the singletons was over 4½ lb. to 10½ lb. inclusive.

No relationship was found to exist between the birth weight of the 154 infants and the volume of the specimens recovered, the *p*H of the specimens, or the incidence of achlorhydria.

In 115 infants, i.e. 74%, free hydrochloric acid was present.

No relationship was found between the birth weight of this group of infants and the volume of the free acidity expressed as ml. of N/10 H.Cl in 100 ml. of gastric contents.

The presence of free hydrochloric acid is recorded in two singletons in the birth weight group over 3 lb. to 3½ lb. inclusive.

I would express my indebtedness to Mrs. Lili Stein, of the Department of Public Health and Social Medicine in the University of Edinburgh, for the statistical calculations used in this article.

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PERFORATED PEPTIC ULCER IN A MONGOLOID INFANT ASSOCIATED WITH CONGENITAL DIAPHRAGMATIC HERNIA

BY

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Peptic ulcers are not common in childhood. According to Hutchins, quoted by Margolis, Valdes-Dapena, and Boles (1949) only 243 cases had been recorded in the literature up to 1944, and 77 of these had perforated. Margolis described perforation of a duodenal ulcer in an infant only 1 month old. In a further search of the literature during the past 10 years we have traced 13 reports of peptic ulcers occurring in children below the age of 7 years; seven were situated in the duodenum and, of these, four had perforated; the remainder were gastric and all had perforated.

Lee and Wells (1923) describe an example of hour-glass stomach in a 13-day-old infant suffering from pyloric obstruction. At operation a chronic ulcer in which a previous perforation had been sealed, was found and later confirmed by necropsy and histological section. The authors, who reported their case under the title *Perforation in utero of a Gastric Ulcer*, considered that the ulcer had been present from before birth, and symptoms and signs became manifest after taking food. Strayer (1949) described a baby, 24 hours old, with ' coffee ground ' vomiting, in whom immediate operation revealed perforation of a duodenal ulcer. This patient died on the seventh day, and at necropsy bilateral hydronephrosis was also found.

Margolis points out that peptic ulceration in infants is usually acute, terminating suddenly with haemorrhage or perforation. Premonitory symptoms, such as anorexia, abdominal pain, haematemesis, or melaena may be present over a period of weeks or months. Pyloric obstruction is seen occasionally and a mistaken diagnosis of congenital hypertrophic pyloric stenosis may be made.

Various aetiological factors have been incriminated from time to time. It has been suggested that asphyxia, resulting from prolonged and difficult labour, may produce a circulatory disturbance with devitalization and consequent ulceration of the gastric mucosa; and the absence of inflammatory reaction is thought to favour this view. Gastric irritants, infection, and malnutrition have all been invoked as possible causative factors, and Berglund (1929) reported six cases of meningitis associated with peptic ulcer. Finally, clinical and experimental observations have long associated peptic ulceration with lesions of the hypothalamus. Mossberger (1947) described a minute tumour which he found immediately anterior to the mamillary bodies in a 5-day-old infant which died of perforated duodenal ulcer. The tumour arose, apparently, from the floor of the fourth ventricle and in structure it resembled pineal gland. The acute ulcer associated with severe burns in children is well recognized, and has been ascribed either to the initial shock or to absorption of toxins from the infected area of skin.

In the case now presented there did not appear to be any particular aetiological factor to account for the ulceration and perforation of the duodenum. No lesion was found in the central nervous system, and the fact that the patient was a mongoloid defective is unlikely to have had any bearing on the problem. He was known to have a severe and overwhelming respiratory infection and the diaphragmatic hernia was probably an incidental finding.

Case History

B.D., a boy aged 4 years and 4 months, was the thirteenth in a family of 14 children who were all alive and well, the eldest being 28 and the youngest 3 years of age. Birth was at full term, the delivery was normal, and the birth weight 8 lb. 12 oz.; he was breast-fed for the first two months and given dried milk feeds with adequate additional vitamins subsequently. Progress

was slow: he sat up at 12 months, stood at 18 months, walked at 2 years, and was able to feed himself at 2½ years. His vocabulary was limited to single words.

Past Illnesses. During early infancy he suffered from repeated attacks of bronchitis and conjunctivitis and was admitted to hospital for short periods on three separate occasions with burns of the left arm, cellulitis of the left leg, and suspected poisoning.

Present Illness. On the present occasion he was first admitted to another children's hospital on September 7, 1950, with a two days' history of diarrhoea and vomiting, and was transferred on September 9, 1950, to an isolation cubicle at Alder Hey Children's Hospital.

Clinical Examination. On admission he was an undernourished child, weighing 23½ lb., and he had the typical appearance of mongoloid deficiency. The temperature was 101° F., pulse rate 140 per minute, respiration rate 36 per minute, and there were signs of extensive bronchopneumonia in both lungs. The heart sounds were obscured, and no abnormalities were found on examination of the ears, throat, abdomen, or central nervous system.

Progress. Treatment was at once begun with sulphonamides and penicillin. Oral feeding was given for 24 hours, but vomiting occurred and necessitated intravenous fluid replacement with an infusion of half-strength plasma with Hartmann's solution, followed by Darrow's solution, half-strength saline, and 5% dextrose —a total of 2,500 ml. in 36 hours. Oral feeding was resumed with difficulty and supplemented with oesophageal tube feeds. The stools were relaxed but not more than two or three were passed each day. No pathogenic organisms were isolated from the faeces.

On September 13, 1950, at 12.10 a.m. about 5 oz. of bright red blood was passed by rectum. At 6.45 a.m. he again passed a small quantity of blood. Later in the day the stools were relaxed and almost black, suggesting that bleeding was still occurring in the upper part of the alimentary tract. On examination the abdomen was moderately distended but there was no muscle guarding and no palpable tumour. During the examination of the chest it was thought that bowel sounds could be heard in the precordial region, but the patient's extreme restlessness and numerous moist sounds made it impossible to be certain of this finding. The following diagnostic possibilities were considered.

GASTRO-ENTERITIS. This was the diagnosis under which the patient had been sent into hospital. The stools, although relaxed, had never been offensive. No pathogenic organisms had been isolated, and the bright red blood passed per rectum was not mixed with the faeces.

BLEEDING MECKEL'S DIVERTICULUM. The bleeding from such a lesion is usually profuse: the fact that the blood was bright red at first was in favour of this diagnosis.

INTUSSUSCEPTION. Against this was the absence of a palpable tumour and of mucus in the stool or on the glove finger when a rectal examination was performed.

DIAPHRAGMATIC HERNIA. Ulceration may occur from pressure of the sharp edge of a hernial orifice on some portion of the alimentary tract. Oesophageal ulceration is a common complication of certain types of diaphragmatic herniae.

The patient's pulmonary condition was so serious that it clearly overshadowed the melaena and precluded further investigation at that time. The temperature ranged between 98° and 102° F. and the respiratory rate between 30 and 40 per minute. An antero-posterior

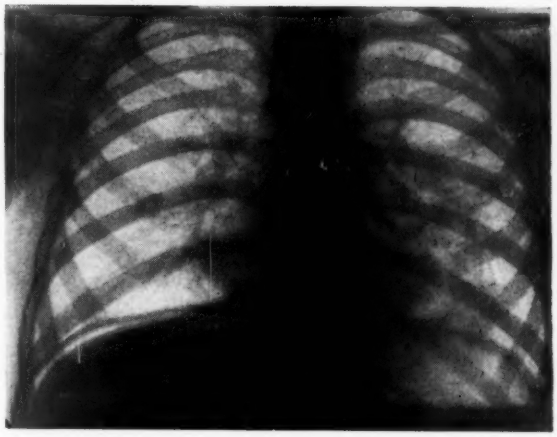

FIG. 1a.—Radiograph showing diaphragmatic hernia and gas shadow under the right side of the diaphragm.

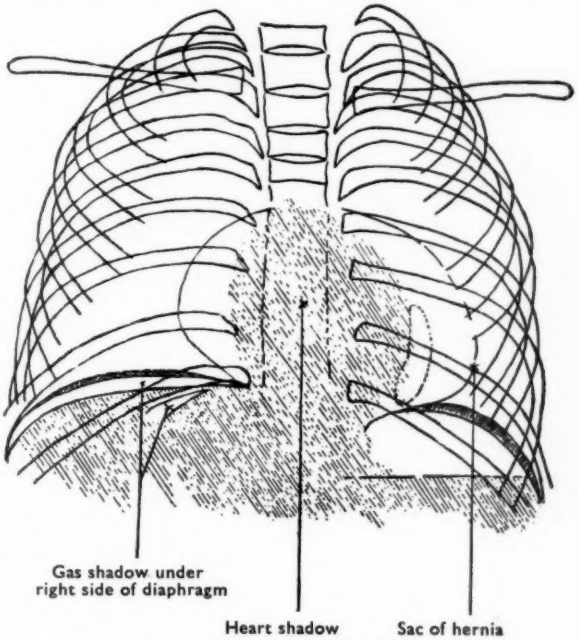

FIG. 1b.—Diagram of Fig. 1a.

radiograph of the chest and abdomen was taken on September 13, 1950, but lateral views and radiographs after a barium meal were postponed until his general condition would justify these procedures. The chest radiograph confirmed the diagnosis of a diaphragmatic hernia and showed the presence of a small amount of air

between the right lobe of the liver and the dome of the diaphragm (Figs. 1a and 1b). The appearance of air above the liver strongly suggested the presence of a perforated hollow viscus, but there was no clinical evidence of a perforation. The abdomen was always relaxed and there was no local tenderness.

On September 14, 1950, his condition was further complicated by the development of whooping cough, with which disease he had been in close contact shortly before admission. The physical signs in the chest became more extensive and his condition deteriorated rapidly. The child died on September 26, 1950. A necropsy examination was carried out by Dr. E. G. Hall.

Necropsy Findings. The body was that of a young boy showing the typical features of mongolism. The heart was small but there were no anatomical abnormalities. A little yellow fluid, from which was cultured coagulase positive *Staphylococcus aureus*, was present in both pleural cavities. The lungs showed bilateral basal bronchopneumonia. The lower half of the oesophagus was dilated and the mucosa necrotic. A diaphragmatic hernia was present through a defect in the anterior leaf of the left half of the diaphragm. The hernial sac, approximately 3 in. in diameter and depth, lay immediately behind the sternum and anterior to the heart; its apex was slightly to the left of the mid-line and reached the level of the manubrio-sternal junction. It contained the middle 9 in. of the transverse colon and corresponding portion of a long mesocolon, but no other viscera. The stomach was normal. On the antero-superior surface of the duodenum there was an acute ulcer, 2 mm. in diameter, which had perforated the wall; the rest of the duodenum was normal. The small intestine was rather short and its mesentery oedematous and fibrotic. There was no evidence of general peritonitis but light, filmy adhesions between the duodenum and the under surface of the liver and a few flecks of inspissated pus over the antero-superior surface of the duodenum were seen. The liver was rotated to the right and the left lobe was smaller than normal. No abnormalities were found in the pancreas, spleen, thymus, kidneys, adrenals, or central nervous system.

HISTOLOGICAL SECTION OF THE DUODENUM. The peritoneal epithelium was destroyed around the ulcer and replaced by a relatively acellular, loose, fibrinous granulation tissue containing degenerated polymorphs. Extending into this tissue from the oedematous subserosa were newly-formed capillaries. The subserosa was infiltrated with lymphocytes, plasma cells, and some eosinophils. The muscle layer at the edge of the ulcer tailed into material similar to that on the serous surface; internally there was a well-defined granulation tissue zone.

Comment

This patient, aged 4 years and 4 months, presenting the typical appearance of a mongoloid defective, was admitted to hospital on account of diarrhoea and vomiting and died after an illness lasting 21 days. The primary cause of death was bronchopneumonia, recognized clinically and confirmed at necropsy. A diagnosis of diaphragmatic hernia was made and, on radiological grounds, perforation of a hollow viscus was suspected; this proved to be due to a perforated acute duodenal erosion. It is interesting to consider how these various findings could be related.

It is obvious that in a patient suffering from bronchopneumonia a large diaphragmatic hernia must diminish considerably the chances of recovery. In fact, a diaphragmatic hernia may attract attention to itself on account of respiratory distress. The additional strain of the paroxysms of whooping cough, together with bronchopneumonia and the associated hernia, are sufficient to account for the unfavourable progress and outcome. The initial symptoms of diarrhoea and vomiting, the subsequent passage of blood by rectum, and the unexpected finding of a perforated duodenal ulcer are less easy to fit into the picture.

The problem can be approached from two angles: the incidence of peptic ulceration complicating diaphragmatic hernia; and the incidence of peptic ulceration in childhood.

Although there is evidence that gastric ulceration can be associated with a diaphragmatic hernia, there seems to be no known association between herniation and duodenal ulcers. Dunhill (1948), in 52 consecutive cases of diaphragmatic hernia at all ages, states that in seven cases (14%) bleeding, caused by venous congestion in the gastric mucosa, occurred. In only one case was a chronic gastric ulcer found. In a further 30 cases described by Harrington (1945) eight had haemorrhage from the stomach and, at operation, seven of these were, in the author's opinion, due to trauma at the edge of the diaphragmatic hernia.

Perforation of a gastric ulcer into a diaphragmatic hernial sac has been described by Lennox Gordon (1916). The patient, aged 56 years, gave a four-year history of indigestion and had been unfit for work for six months. He had had abdominal pain, vomiting, and constipation for four days before admission to hospital. Liver dullness was absent and the right chest was hyper-resonant. Death occurred before operation, and at necropsy a defect in the right dome of the diaphragm with a diaphragmatic hernia, containing the pyloric half of the stomach, the first and second parts of the duodenum, the right half of the transverse colon, and some coils of small intestine, was found. A perforation of the anterior wall of the stomach 1 in. from the pylorus had occurred, and this perforation had all the characteristics of an ulcer and seemed to have been of recent origin. Sangster (1936) reports the post-mortem findings in the case of a man aged 64 years, who had a defect of the left dome of the diaphragm. The hernia contained

the left lobe of the liver, a portion of the transverse colon, and loops of the jejunum in addition to the stomach, which was rotated so that the greater was higher than the lesser curvature. A perforation of the posterior wall of the stomach had occurred into the left pleural cavity.

There is no evidence of any association between the duodenal ulcer and the diaphragmatic hernia in the case now reported. The ulcer was of the acute variety and there is no reason to incriminate the diaphragmatic hernia which had presumably been present since birth. The hernia, moreover, was a ventral one through the left hiatus of Morgagni and contained only a portion of the transverse colon. The neck of the hernia was wide and there had been no strangulation; nor was there any evidence to suggest that there had ever been any other contents. Peptic ulceration, when it occurs in association with a diaphragmatic hernia, is usually gastric in site and of chronic type, and it arises when part of the stomach is itself within the hernial sac.

Summary

A clinical case of a typical mongoloid defective, aged 4 years and 4 months, is presented. He was admitted to hospital on account of diarrhoea and vomiting. A diaphragmatic hernia was discovered. Death occurred from bronchopneumonia complicated by whooping cough. Necropsy demonstrated perforation of a duodenal ulcer. The relationship between peptic ulceration and diaphragmatic hernia is considered and the incidence of peptic ulceration in infancy briefly discussed.

We should like to thank Professor N. B. Capon, Professor of Child Health, for his helpful criticism and advice, Dr. E. G. Hall for his necropsy report, and Dr. W. E. Crosbie, medical superintendent, for permission to publish this paper.

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THE RELATIONSHIP OF CYSTIC LESIONS OF THE ACINI OF THE PANCREAS TO AGE, CAUSE OF DEATH, AND FIBROCYSTIC DISEASE IN CHILDREN

BY

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Dilated plugged acini in the pancreas are one of the fundamental histological features in 'fibrocystic disease.' Andersen (1938), however, in her original article on 'Fibrocystic Disease in the Pancreas in Relation to Celiac Syndrome' pointed out that cystic acini occur in a large number of children, and she was careful to confine her diagnosis of fibrocystic disease to cases where more than 90% of the acini of the gland were affected.

Following Andersen's work there has been an increased interest in the presence of cystic changes in the acini of the pancreas, and lesions have been described in a number of apparently quite different conditions. Baggenstoss (1947, 1948a and b) described a high incidence of plugged acini in chronic nephritis, hypertension, uraemia, ulcerative colitis, and intestinal obstruction; Mallory (1947) in severe infections and in all of 24 cases of typhus; Gillman and Gillman (1945) found the lesion in malnutrition in South Africa; Wallace and Ashworth (1942) and Andrew (1944) in old age; and Hartz (1948) in patients dying after starvation. Relatively little interest appears to have been taken in the significance of these plugged acini in children not showing the full fibrocystic syndrome. An attempt has been made here to determine the incidence of plugged and cystic acini in the pancreas of children at necropsy, and to relate these lesions to the clinical disease and age of the children.

Material and Methods

Blocks were taken from the head and tail of the pancreas of children coming to necropsy at the Sheffield Children's Hospital during the years 1947-50. Sections were stained with haemotoxylin and eosin and also with Masson's trichrome. With the latter stain the colloids in dilated acini frequently take on a different colour from that of the surrounding cells, making the plugged acini much more easily identifiable than in a haemotoxylin-eosin preparation. All glands were excluded which showed gross post-mortem autolysis, or had been affected by extensive lesions such as tumour infiltration or haemorrhage. The number of glands remaining and analysed from 400 necropsies was 310.

The clinical features recorded were the age of the child, duration of illness, cause of death, presence or absence of staphylococcal infection, and the major disease causing death.

The glands were divided into four groups: (1) showing fibrocystic disease in which the majority of acini were affected and corresponding to the lesions described by Andersen (1938); (2) in which plugged acini were readily identified on the sections and were a prominent feature of the pancreas, although affecting less than 90% of the acini; (3) cases in which plugged acini were found in small numbers affecting less than 1% of the acini; (4) no lesions.

For this survey a pancreas was reported as negative if plugged acini were not found in at least two complete cross sections taken from different parts of the gland.

Results

Of the 310 glands examined, fully developed fibrocystic disease was present in 11 (3·5%) cases; large numbers of plugged acini were found in 23 (7·5%); and in small numbers in a further 110 (35·5%). The total number of glands showing lesions was 144 (41·5%) and those with no lesions 166 (58·5%).

The cases were divided into age groups (Fig. 1). The first group (*a*) comprised stillborn infants and those dying during the first week after birth. (It was thought unjustified to subdivide this age period.) The other cases were divided into groups of approximately the same number: (*b*) 29 cases aged 1 to 4 weeks; (*c*) 41, aged 1 to 3 months; (*d*) 25, aged 3 months to 6 months; (*e*) 32, aged 6 months to 9 months; (*f*) 34, aged 9 to 18 months;

(*g*) 46, aged 18 months to 3 years; (*h*) 43, aged 3 years to 8 years; and (*i*) 17, aged over 8 years. When the percentage of organs showing lesions in these groups was compared (Fig. 1) a fairly uniform fall

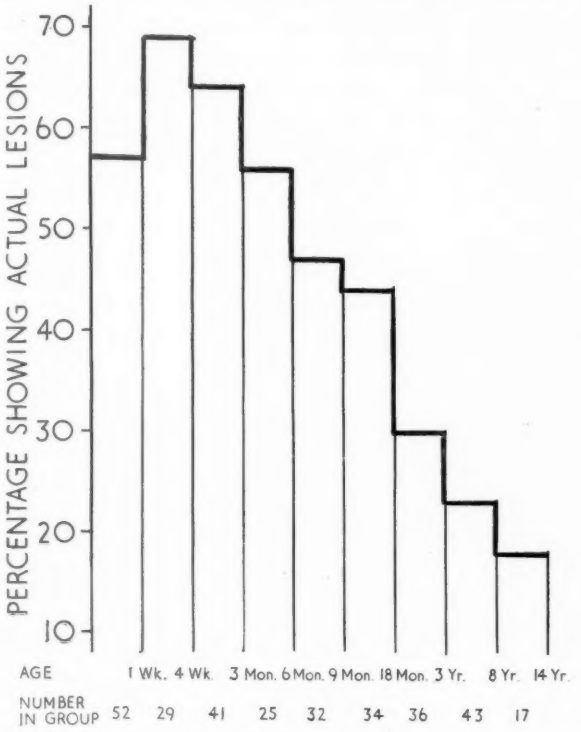

FIG. 1.—Diagram showing the percentage incidence of acinal lesions in different age groups.

in incidence was found: (*a*) 57%, (*b*) 69%, (*c*) 64%, (*d*) 56%, (*e*) 47%, (*f*) 44%, (*g*) 30%, and (*i*) 18%, giving a statistically significant difference between the first and last two groups.

Classified according to duration of illness the following results were obtained. Of 43 cases dying within the first 24 hours, 17 (42%) showed plugged acini; of 50 cases dying between one and five days, 23 (46%) had lesions; of 37 cases dying between six and 14 days, 17 (46%); of 26 dying between 15 and 32 days, 16 (61%); and in the largest group, 136, in which the duration of illness was over one month, 64 (47%) lesions were found. It was felt that there was no significant difference between these groups.

Although minor respiratory infections were present in a large number of instances there were 69 cases when this was the primary cause of death. Twenty-two of these were staphylococcal infections, and the remaining 47 were due to other organisms. Fourteen (63%) of the staphylococcal group showed plugged acini compared with 23 (48%) of the others.

Sixty-one cases had gross congenital deformities, and 41 (67%) of these had plugged acini. The disease with the lowest number of plugs was tuberculosis with an incidence of 18% (eight of 44 cases). Other diseases provided too small numbers to give figures useful for comparison.

Discussion

The finding of plugged acini (Figs. 2 and 3) in 46% of the children was an unexpectedly high figure, but this was less than the incidence (52%) found by Baggenstoss (1948a) in uraemia. Andersen in her original paper examined sections of the pancreas in 605 cases from 1,000 necropsies. She found 20 cases (3·3%) in which 90% or more of the pancreas was involved, 21 cases (3·5%) in which 20-30% was involved, and 69 cases (11·4%) in

FIG. 2.

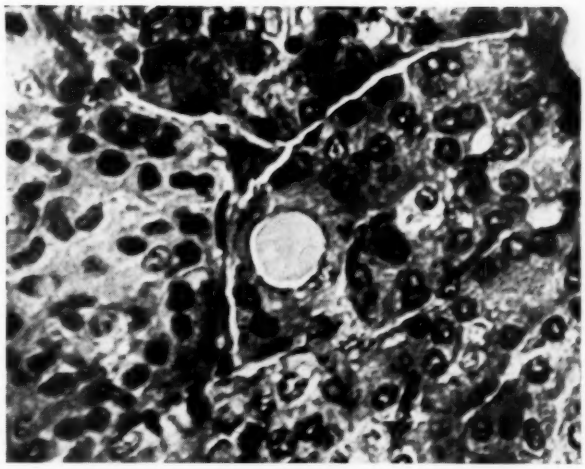

FIG. 3.

FIGS. 2 and 3.—Microphotographs showing isolated cystic acini in otherwise normal pancreatic glands.
Fig. 2 × 490. Haematoxylin and eosin.
Fig. 3 × 590. Haematoxylin and eosin.

which smaller numbers of cysts were found. In view of the finding in the present series that the incidence of plugged acini varies greatly with the age of the child, it will be obvious that it is not profitable to compare figures unless they are confined to narrow age groups. If in the present series the children under 18 months are excluded, the incidence of lesions is approximately 30%, which may then be compared with the incidence of 18·2% in Andersen's series. It would seem that the differences with Andersen's figures could be explained by age and chance, and also by the fact that in the present series a definite search was made for the minimal lesions, whereas Andersen's chief concern was with the gross lesion of the fibrocystic syndrome.

The variation with age (Fig. 1) found in the present study appears to be much greater than could be accounted for by chance. Whether the lesions appear with even greater frequency before birth I am unable to say, as in the five foetal pancreatic glands available to me between the ages of 4 to 8 months lesions were found in only one, but post-mortem changes limited critical histological comment. The incidence of lesions in the pancreas seems to parallel the rate of growth of the child. It was shown by Gillman, Gillman, Mandelstam, and Gilbert (1945) and by Kristal (1947) that fibrosis of the liver and pancreatic lesions could be produced much more readily in growing than in mature rats when fed on a diet deficient in protein. It is well known that deficiency states are most liable to occur in growing animals. The incidence (18%) of acinar plugs in older children is comparable with the 20% found in adults by Baggenstoss in his control series. It is notable that the incidence of the plugged acini shows a parallel age incidence to fibrocystic disease (Andersen, 1938), and that it is not until later in childhood that the general histological appearance of the pancreas is similar to that in the adult (Emery, 1951).

Andersen found a number of pancreatic glands (15%) in which lesions similar to those in fibrocystic disease were present and in which the children showed no symptoms of the latter syndrome. Blackfan and May (1938) found 200 cases with minor asymptomatic lesions in a series containing 35 full lesions. The same occurred in the present series; a large number of glands had minimal lesions (110), a few noticeable lesions (23), all being symptomless, and a small number (11) with the full fibrocystic syndrome. Degrees of the fibrocystic syndrome do occur clinically (Gibbs, Bostick, and Smith, 1950). Farber (1944) considers that these acinal lesions themselves produce the grossly scarred and fibrotic gland. It seems that the fibrocystic disease syndrome may be the end stage of a disorder which is present in a large number of infants and which is progressive in some, as yet, unrecognized circumstances. It is notable that on genetic grounds Lowe, May, and Reed (1949) state that a recessive hereditary factor for fibrocystic disease is present in 2 to 18% of the general population.

The varied incidence of plugged acini with age was found to interfere greatly with attempts to relate the lesion with particular diseases or incidents. The diseases which showed the lowest incidence of acinar lesions were tuberculous meningitis and miliary tuberculosis, in which lesions were found in only eight (18%) of 44 cases, but the average age at death of these cases was 4 years 10 months, which makes the incidence not significantly different from the general incidence (23%) for children of this age. Similar difficulties were found when comparing other diseases such as staphylococcal and other infections. It is obvious that very large series of cases of identical age groups would be necessary in order to prove differences in disease incidence.

There appears to be an incidence of plugged pancreatic acini in between 10 and 20% of general necropsies. Baggenstoss found the lesions in 20% of 100 controls in his nephritis series and Menten and Kinsey (1949) found cysts in 35 of 256 necropsies not associated with any particular disease or age, and Mallory (1947) in 10% of post-mortem material in Italy in World War II. If we exclude the finding of cystic areas in association with surgical lesions of the pancreas, e.g. tumours, stones, and congenital deformities, an increased incidence of plugged acini has been reported in association with several apparently diverse conditions. There is an increase in old age both in man and dogs (Wallace and Ashworth, 1942), and in senile rats (Andrew, 1944); in nephritis and renal failure (Baggenstoss, 1947); and Ball, Baggenstoss, and Bargen (1950) found an incidence of 53% in 91 cases of ulcerative colitis. The lesion occurs in severe wasting disease in the Bantu (Gillman and Gillman, 1945). Mallory (1947) reported that he found lesions in all of a series of 24 necropsies in typhus. All of the above conditions, with the exception of senility, appear to be associated with a severe nutritional upset. Waterlow (1948), however, did not find lesions in the pancreas in children with severe malnutrition in the West Indies, or Davies (1948) in Uganda, but their histological material does not appear to have been good. In growing rats a diet low in protein produces cystic lesions in the pancreas very like the lesion in fibrocystic disease (Kristal, 1947; Véghelyi, Kemény, Pozsonyi, and Sos, 1950). Friedman and Friedman (1946) produced similar lesions in rats with a high fat, low protein diet.

The only vitamin deficiency which produces lesions in the pancreas is vitamin A, and lesions produced by this means have been described in children (Wilson and DuBois, 1923; Wolbach and Howe, 1925), but the aetiology in these cases is not entirely convincing and Andersen (1949) was unable to produce the lesion in neonatal rats when developed on a diet deficient in vitamin A.

An entirely different approach, that of stimulating the vagus and administrating pancreozymin, has been shown to produce colloidal material in pancreatic acini in cats (Babkin, Rubaschkin, and Ssawitsch, 1909; Sergeyeva, 1938; and others), although this was not confirmed by Harper and Mackay (1948). Ramsay, Thomas, and Crider (1943) produced the same change by administering peptone directly into the duodenum and small bowel. These stimulative effects on the pancreas produce thin, thread-like material in the acini and ducts and a picture similar to that seen in some of the illustrations of normal pancreas in the old German literature (Stangl, 1901). These changes are not similar to the lesions described in this paper but they do indicate a method of production of inspissated secretion.

The conclusion appears to be that lesions of the acini of the pancreas most resembling those in children are associated in man with disorders of the intestinal tract, particularly those associated with wasting and disease where protein metabolism is grossly upset. The observation of Tarver and Schmidt (1942) that the cells most actively handling protein are those of the pancreas and the intestinal mucosa suggest that these cells may be most readily disorganized as a result of protein deficiency.

It is tempting to postulate that the increased incidence of plugged acini found in children in their most active growing period is related to their relatively enhanced nutritional requirements at that time.

Summary

The pancreas has been examined histologically for the presence of plugged and cystic acini in 310 necropsies at the Children's Hospital, Sheffield.

Cysts were found in 144 (46·5%) of the cases; in small numbers in 110 (35·5%) cases, in larger numbers in 23 (7·5%) cases, and in the frank fibrocystic syndrome in 11 (3·5%).

It was found that there was a marked variation of incidence with age, the incidence under six months being over 60% and falling to the adult level of about 20% by the age of 9 years.

It was found that the varying incidence with age eliminated differences in incidence apparently associated with different diseases.

After considering the experimental and other causes of cystic lesions in the acini of the pancreas it is suggested that the high incidence of cysts in the period of most active growth may be related to the child's enhanced protein requirements at that period.

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GANGRENE OF THE FOREARM IN THE NEWBORN

BY

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This case is reported on account of its rarity, and also because it exhibited several interesting features. No similar case has been seen among 18,000 babies delivered in the maternity unit of Dudley Road Hospital, Birmingham.

Case History

A primigravida aged 24 was first seen at the antenatal clinic on September 12, 1949, in the twentieth week of pregnancy. Physical examination revealed no abnormalities. The blood Wassermann reaction was negative. The blood group was A, Rh positive. At a further examination on January 18, 1950, a normal vertex presentation was confirmed, but she now had well marked oedema of the ankles, and the urine contained albumin. The blood pressure was 135/85. She was admitted with a mild toxaemia two days later, in the thirty-eighth week of pregnancy. The following day the urine contained 6 g. albumin per litre (Esbach), and the blood pressure was 140/95. Surgical induction was therefore performed on January 22, and a live male infant of 7 lb. 9 oz. (3,430 g.) was delivered within 12 hours. After clearing the air passages, the baby cried well, and appeared to be normal in every way apart from the condition of the left forearm, which was motionless, cold, and discoloured.

We first saw the baby two hours after birth. His general condition was good and his cry was strong. The left arm lay limply by his side, but the opposite arm moved normally. The skin of the forearm was a dirty ivory colour, and there was a deep constriction mark just above the elbow. The whole forearm was cold, and no pulse was felt at wrist or elbow. Although we failed to recognize its significance at the time, we observed that the lower extremities were cyanosed, whilst the head, trunk and right arm were pink. Auscultation of the heart and lungs revealed no abnormality.

Treatment. Conservative treatment was advised, but by the following day the baby's condition had deteriorated. He was pale, lethargic, and reluctant to feed. In the affected arm, the constriction mark at the elbow was less noticeable, but the colour changes of gangrene were appearing, and the skin was leathery and dry. Amputation was therefore performed under general anaesthesia, the limb being removed one inch above the elbow on January 23. The underlying muscle had the consistency of liver. It was striking that the brachial artery bled freely before ligation.

The next morning, January 24, the baby was very much worse. He had vomited once or twice during the night, was jaundiced and cyanotic, with a diffuse petechial rash over the face, neck, and shoulders. The cry was still strong, however, the heart beat was forceful though rapid, and the lungs were clear. He was placed in an oxygen tent, oral penicillin was replaced by three-hourly injections of 20,000 units, vitamin K ('synkavit'), mg. 10, was given every 12 hours, and feeds of lactose water were offered every three hours. By evening the temperature had risen to 100·4° F. and the general condition appeared unchanged. The wound was perfectly clean and dry. At 6 a.m. on January 25 the baby suddenly collapsed. The respirations became rapid and grunting. The whole body was covered with purpura consisting of diffuse petechial haemorrhages intermingled with large ecchymoses, and there were also subconjunctival haemorrhages. Jaundice had increased; the abdomen was distended and tympanitic; the pulse was regular (100/minute); and there were fine râles at both lung bases. He died at 11.15 a.m.

Necropsy. The umbilical cord was clean and dry. The amputation wound was clean. The trachea and bronchi were clear. The lungs were only slightly aerated, the left more than the right. A number of asphyxial haemorrhages were seen beneath the pleura. The pericardium contained an excess of bile-stained fluid. The heart was enlarged, due to dilatation of the right side. There was a large ante-mortem thrombus within the auricle of the left atrium. The foramen ovale was patent, but well closed by a valve-like flap. The mitral valve showed hyperaemia of the cusps on which were numerous small blood cysts but no vegetations. The aortic and pulmonary valves had rather pink cusps, but otherwise appeared normal. The cusps of the tricuspid valve were also rather hyperaemic. The arch of the aorta at the point from which the left subclavian artery was given off, was almost completely obstructed by a large thrombus, which also blocked the left subclavian artery. No other branch of the aorta was blocked. The ductus arteriosus was widely patent and apparently maintained the blood stream to the descending aorta. In the head and abdomen no significant abnormalities were found apart from appearances in the liver suggestive of toxaemia. Dissection of the amputated limb revealed no abnormality of the large vessels.

Discussion

Gangrene of an extremity in the newborn infant has rarely been reported, and we have been able to

FIG. 1. Infant 24 hours after birth.

trace records of only 46 cases. When Heller and Alvari (1941) reviewed the literature on the subject, they stated that 40 cases, including their own, had been reported up to that time. Steiner (1945), in describing a further case, drew attention to two cases omitted by those authors. Another case was recorded by Caritat, Solovey, and Bonaba (1945), and Leveuf, Laurence, and Mallet (1947) described a case of their own, and referred to a very similar case of Ombrédanne and Lacassie (1930).

In many of the recorded cases, trauma at delivery has seemed a likely explanation of the gangrene, especially in those cases where labour was difficult or abnormal. Pressure necrosis of a prolapsed extremity, similar to that which may occur on the scalp, has been advanced as a possible mechanism in some cases. This is confidently given as the cause of the gangrene in Steiner's case, in which the prolapsed hand was caught between the head and the bony pelvis. In this case no thrombosis was found in the vessels of the amputated extremity. In a similar case described by Fischer (1929), however, death occurred on the fourteenth day, and necropsy revealed thrombosis in the great vessels of the affected arm, pulmonary arteries, and aorta. Thrombosis in this case may well have been a sequel to infection. Heller and Alvari were able to divide the majority of cases broadly into two categories; those which could be attributed to trauma, and those in which infection was the most likely cause. Their own case occurred after a difficult forceps delivery following a prolonged labour, and they had good reason to assume that pressure at some point on the affected limb was responsible for the ensuing gangrene. Since the axillary artery was initially pulseless and yet pulsated normally on the sixth day, they postulated that 'there existed a temporary agglutination of the intimal surfaces of the large vessel . . . similar to that which occurs when a piece of rubber tubing of equivalent calibre is pressed on firmly for a protracted period,' which is certainly an ingenious hypothesis. They were unwilling to consider rapid development of a collateral circulation because the axillary artery resumed pulsation six days after birth. But it should be emphasized that the numerous anastomoses around the neck and shoulder girdle may allow a return of pulsation in the axillary artery when, for instance, the first part of the subclavian artery is obstructed. Thrombosis seems more likely than 'intimal agglutination'.

In our own case the cause of gangrene is not as obvious as the post-mortem findings would suggest. Although a definite thrombus occluded the mouth of the subclavian artery, nevertheless, at operation, the brachial artery had bled freely, thereby demonstrating an adequate collateral circulation. On the other hand, the constriction band above the elbow was highly suggestive of pre-existing pressure *in utero*. The evidence, we feel, is in favour of a dual mechanism—primary impairment of circulation due to thrombosis which was then aggravated secondarily by local pressure at the elbow. The position of the thrombus, at the point where the subclavian artery is given off, strongly suggested that it was embolic, and the ante-mortem thrombus in the left auricular appendage provided a possible source. There was

FIG. 2.—Gangrenous left forearm. Constriction mark at upper limit of gangrene can be seen.

no sign of foetal endocarditis, and no obvious abnormality to explain thrombus formation in the atrium. It is possible that stasis in a dilated atrium of a failing heart might be sufficient to encourage thrombus formation, yet in this heart the main stress had been upon the right side and, although the right atrium was greatly dilated, there was no thrombus there. Morison (1945) has described a peculiar form of arteritis occurring in the aorta of a newborn baby and leading to thrombosis. Unfortunately we were unaware of this at the time and no histological examination of the wall of the aorta was made.

An interesting feature of this case was the alteration in circulation brought about by the obstruction in the aorta (Fig. 3). It simulated exactly the circulation in the infantile type of coarctation of the aorta, and in this anomaly cyanosis of the lower limbs with a normal colour of the upper extremities, which we had noticed in our case, is one of the diagnostic features. The relative enlargement of the right side of the heart is also attributable to this altered circulation.

From the surgical point of view, these cases raise several problems, as each case reported appears to differ from the others. There seems to be no common aetiology, and treatment must be based on the findings in each individual case. The variety of causes listed defies any attempt at precise classification, but that of von Khautz (1914) probably provides the best working basis. Undoubtedly, in many cases conservative treatment is indicated because of the uncertainty as to the pathology, and the remarkable recuperative powers of the infantile circulation and tissues. In this case there was no doubt of the necessity for amputation, though it may be questioned whether an immediate operation was indicated. Two or three days delay in a condition of dry gangrene might have allowed for a more intensive course of antibiotics.

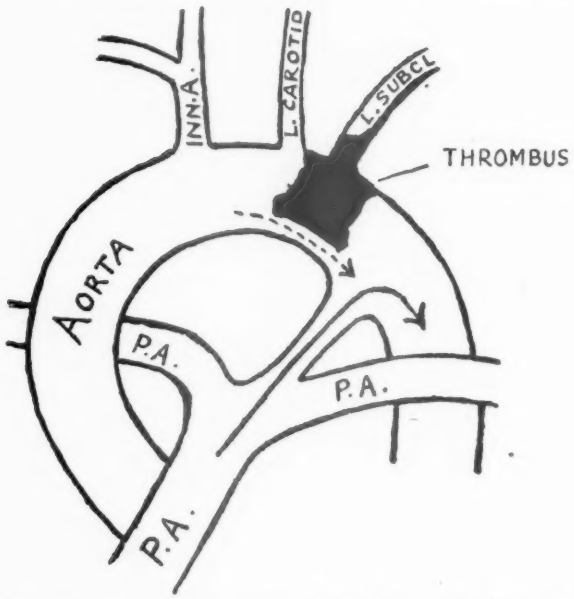

FIG. 3.—Diagram showing thrombus occluding left subclavian artery and leaving only a narrow channel in the aorta. Heavy arrow shows main blood flow to descending aorta from pulmonary artery through patent ductus arteriosus.

Summary

A case of gangrene of the left forearm in a newborn infant is described. In spite of amputation on the second day, the baby developed a fatal toxaemia.

At necropsy, thrombosis was found in the aorta obstructing the mouth of the left subclavian artery. The blood stream in the descending aorta beyond the obstruction came from the right ventricle via the pulmonary artery and a widely patent ductus arteriosus, thereby simulating the altered circulation seen in the infantile type of coarctation of the aorta. The thrombus was thought to have originated by

embolism from ante-mortem thrombus in the left auricular appendage.

The possibility of local pressure as an immediate cause of the gangrene is considered.

Forty-six cases of gangrene in the newborn have been traced in the literature, some of which have been briefly discussed.

We should like to thank Dr. B. T. Davis for his report on the findings at necropsy, and Dr. M. E. Disney for helpful criticism and advice.

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FAMILIAL INCIDENCE OF NON-LIPOID RETICULO-ENDOTHELIOSIS (LETTERER-SIWE DISEASE)

BY

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Letterer (1924) described the case of a child of 6½ months who was admitted to hospital with fever, generalized lymphadenopathy, an enlarged liver and spleen, a petechial rash, and anaemia. The child died four days after admission, and on microscopic examination, Letterer found that the architecture of the spleen and lymph nodes was destroyed and these organs were diffusely infiltrated by large clear histiocytic cells. The liver, bone marrow and skin showed similar changes.

Siwe (1933) recorded the case of a girl of 16 months. He found three other cases of this condition in the literature. In his description of the disease, he stressed that it was neither familial nor hereditary, that it occurred exclusively in early childhood and was invariably fatal.

Abt and Denenholz (1936) reviewed nine cases including one of their own and named the condition 'Letterer-Siwe's Disease.' Several reviews of the literature have appeared since then; the most recent are those of Schafer (1949), MacKelvie and Park (1950), Claireaux and Lewis (1950), and Havard, Rather and Faber (1950). Since these were published Veslot, Duperrat, Browaeys, Garnier, and Pley (1950), and Steele (1950) have both reported one case. None of these authors has found a case with familial incidence. The following is a report of two sisters who both died of the disease in early infancy.

Case Reports

Case 1. M.P., a girl aged 3 months, was admitted to the Victoria Hospital for Children, London, on May 4, 1950. She was delivered normally at full term and her birth weight was 8 lb. 4 oz. She appeared healthy until three weeks before admission when her mother noticed that she was becoming increasingly breathless and pale. Two days before admission, the skin of her face had become yellow and her urine was dark.

The patient's family history showed that both parents were in good health. Their firstborn child, a girl, died of anaemia in July, 1944, at the age of 6 weeks. Notes and material for study were kindly provided by the hospital where she died and the case is described below (Case 2). Their second child, a boy, born in 1946, had always thrived and was in good health. There was no history of similar illness among the relatives of either parent.

On admission, the child was seen to be very pale and jaundiced with some oedema. Her weight was 11 lb. 1 oz. The spleen was easily palpable and firm and the liver was felt two fingers' breadth below the costal margin. Only the left tonsillar lymph node was palpable. The haemoglobin was 25% (Haldane) with 1·6 m. R.B.Cs. per c.mm. The W.B.Cs. were 3,100 per c.mm. with the following differential count:

Myelocytes = 5%
Metamyelocytes = 14%
Mature polymorphonuclears = 9%
Monocytes = 28%
Lymphocytes = 38%
Atypical mononuclears = 6%

Two normoblasts were seen in counting 100 leucocytes. The R.B.Cs. were agglutinated by Rh positive (anti-D) serum and the direct Coombs test, the Wassermann and Kahn reactions were all negative. X-ray examination of the arms and legs revealed no bony abnormality.

Throughout her stay in hospital she had a temperature of between 99 and 103° F. She was treated with repeated small blood transfusions and the haemoglobin on the fifth day was 48%. At this time, the platelet count was 28,000 per c.mm. Eight attempts at marrow puncture from the tibia, iliac crest, and sternum were all unsuccessful.

On the fifth day in hospital petechiae appeared on the skin and she began to bleed from the mouth and nose. This continued and the abdomen became distended. On the seventh day and again on the ninth day she had convulsions. She died on May 13, 1950, nine days after admission.

Necropsy. Jaundice was present and there were scattered petechiae on the skin and mucous membranes of the mouth. The heart was normal in size. The muscle was pale and petechiae were found on the endocardium, especially over the papillary muscles. Each pleural cavity contained 120 ml. of clear yellow fluid. The lungs were oedematous. There were enlarged lymph nodes at the bifurcation of the trachea. Scattered

petechiae were present over the mucosa and serosa of the whole alimentary tract. There was a mass of lymph nodes adherent to the duodenum and surrounding the common bile duct but not completely occluding it. The glands were firm, discrete, and greyish red on cut section. The liver was moderately enlarged. It gave a faint reaction for iron with acid ferrocyanide solution. The genito-urinary apparatus and endocrine glands appeared normal. The spleen was five times its normal size and was dark in colour. It gave a similar iron reaction to the liver. The femoral marrow was pale pink in colour and was firm and gritty. There were petechiae in the brain and the grey matter was bile-stained.

On microscopical examination it was observed that the organs were infiltrated with large reticulum cells. These were large round or oval cells with faintly eosinophilic cytoplasm. Most of the nuclei were oval or indented and pale-staining with fine scattered chromatin. Some were rounded and darker. Mitoses were infrequent. The cells were not forming reticulin and no fat was seen in frozen sections stained with Sudan III and IV. Many cells showed active phagocytosis. Some lymphocytes, polymorphonuclears, and plasma cells were present among them.

The sinuses of the spleen were filled with a large number of these cells which were ingesting red blood cells. Often six or eight erythrocytes were present in a single cell (Fig. 1). The Malpighian bodies were small and there were some scattered foci of erythropoiesis. Some free iron was present. The lymph nodes around the pancreas and common bile duct and in the porta hepatis were similarly infiltrated. The follicles were inconspicuous and the lymphatic sinuses contained reticulum cells ingesting lymphocytes and polymorphonuclear cells. In the liver, the infiltration was much less in extent and confined to the portal tracts. There were small foci of erythropoiesis and some free iron. The bone marrow contained large numbers of reticulum cells with greatly reduced haemopoietic tissue. The epiphyses of the vertebral bodies were normal. There was slight infiltration with reticulum cells in the lung, pancreas, and heart muscle.

Case 2. P.P., a girl aged 1 month, was admitted to hospital on July 5, 1944, with pallor and failure to gain weight. She had been born at full term weighing 8 lb. 2 oz. She had been jaundiced for three days in the first week of life and had been discharged after 15 days weighing 8 lb. 1 oz. Four days later, she had been again lightly jaundiced but this had only lasted two days. Since then, her weight had gradually diminished.

On examination she weighed 7 lb. 3½ oz. She was very pale and the liver, spleen, and inguinal glands were palpable. The haemoglobin was 20% with 1·2 m. R.B.Cs. per c.mm. The W.B.Cs. were 5,800 per c.mm. with the following differential count:

Polymorphonuclear cells=8%
Myelocytes=1%
Lymphocytes=79%
Monocytes=9%
Basophils=1%
Nucleated R.B.Cs.=2%

A tibial marrow puncture was attempted but a small amount of blood only was withdrawn. She was treated by blood transfusion but died five days after admission. Her temperature was between 101 and 103° F. until the day before her death when it fell below normal.

Necropsy. The body was very jaundiced. The lungs showed patches of bronchopneumonia. The liver weighed 270 g. and was firm and greenish. The spleen was large. The brain showed no abnormality but there was bile staining of the cerebrospinal fluid. No information was given on the size of the lymph nodes.

Microscopic examination was made on sections of the spleen (Fig. 2), bone marrow, liver, and lung. All the sections showed changes similar to those in Case 1.

Discussion

The sisters whose cases we have reported both died in early infancy with almost identical clinical histories and post-mortem findings. They both appeared to be healthy at birth. The disease began as a rapidly progressive anaemia with hepatosplenomegaly, petechial haemorrhages, and fever. In both, the leucocyte count was low with scanty granulocytes. Large numbers of pale histiocytes were present in the organs, especially the spleen, lymph nodes, and bone marrow. The cells did not contain fat and eosinophils were not present among them.

Erythroblastosis foetalis can be excluded as the disease was not present from birth, the mother was Rh positive, and in Case 1 the direct Coombs test was negative. Dr. R. R. Race has kindly grouped the blood of the father, mother and their surviving child and found them as follows:

Father: O, MsNs, R_2r, Le(a+), Lu(a−), Fy(a+), K−, P+.
Mother: A_1B, MsMs, R_2r, Le(a−), Lu(a+), Fy(a+), K−, P+.
Brother: B, MsMs, R_2r, Le(a−) Lu(a+), Fy(a+), K−, P+.

The serum of the mother tested against the father and the child gave no reaction by the Coombs test, and Dr. Race did not think it likely that the known blood groups could have played a part in the aetiology of the disease.

Repeated Wassermann and Kahn tests on the serum of both parents were all negative. These tests were also negative in Case 1. The diagnoses of leukaemia, Hodgkin's disease, reticulosarcoma, or lipoid reticuloses were excluded by the appearances of the blood and of the tissues at necropsy. Of the nine cases reviewed by Abt and Denenholz (1936) only four had localized bone lesions. Thus the absence of these lesions by no means rules out the diagnosis of Letterer-Siwe disease.

Orchard (1950) described a case in which a

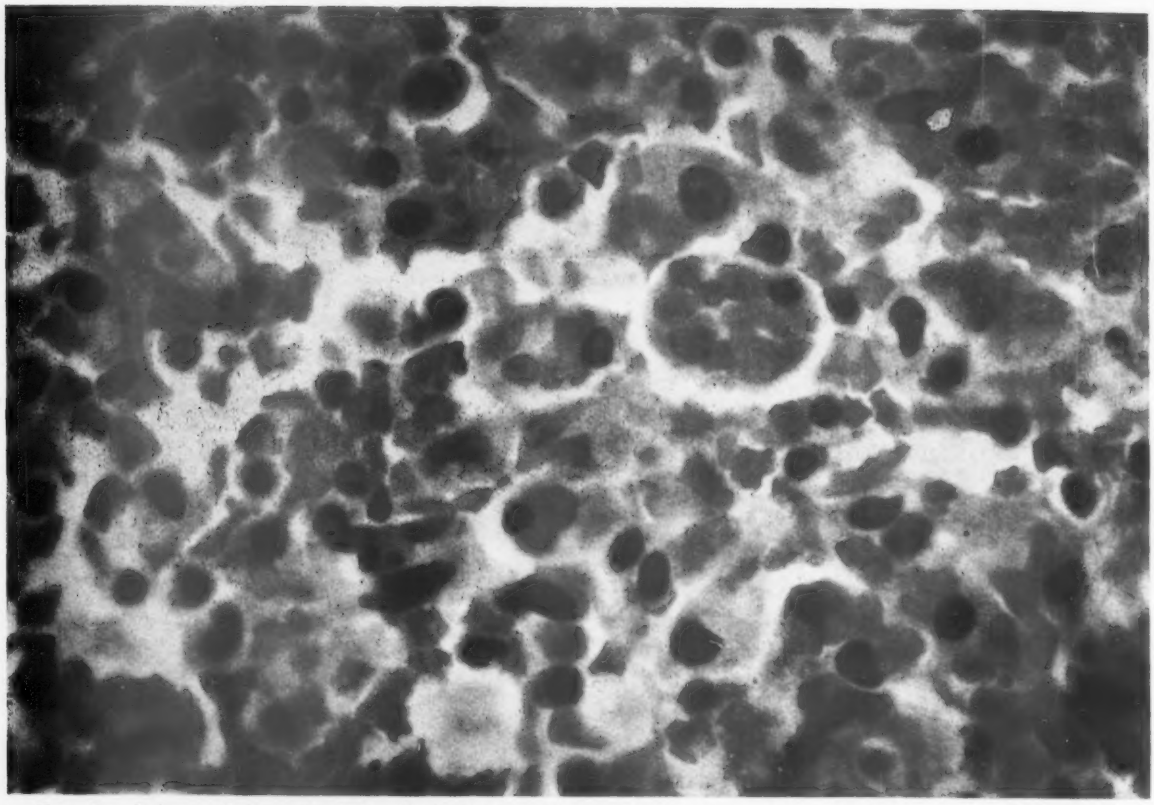

FIG. 1.—Spleen of Case 1 × 800. Stained haemalum, phloxine-tartrazine. Note the erythrophagocytosis.

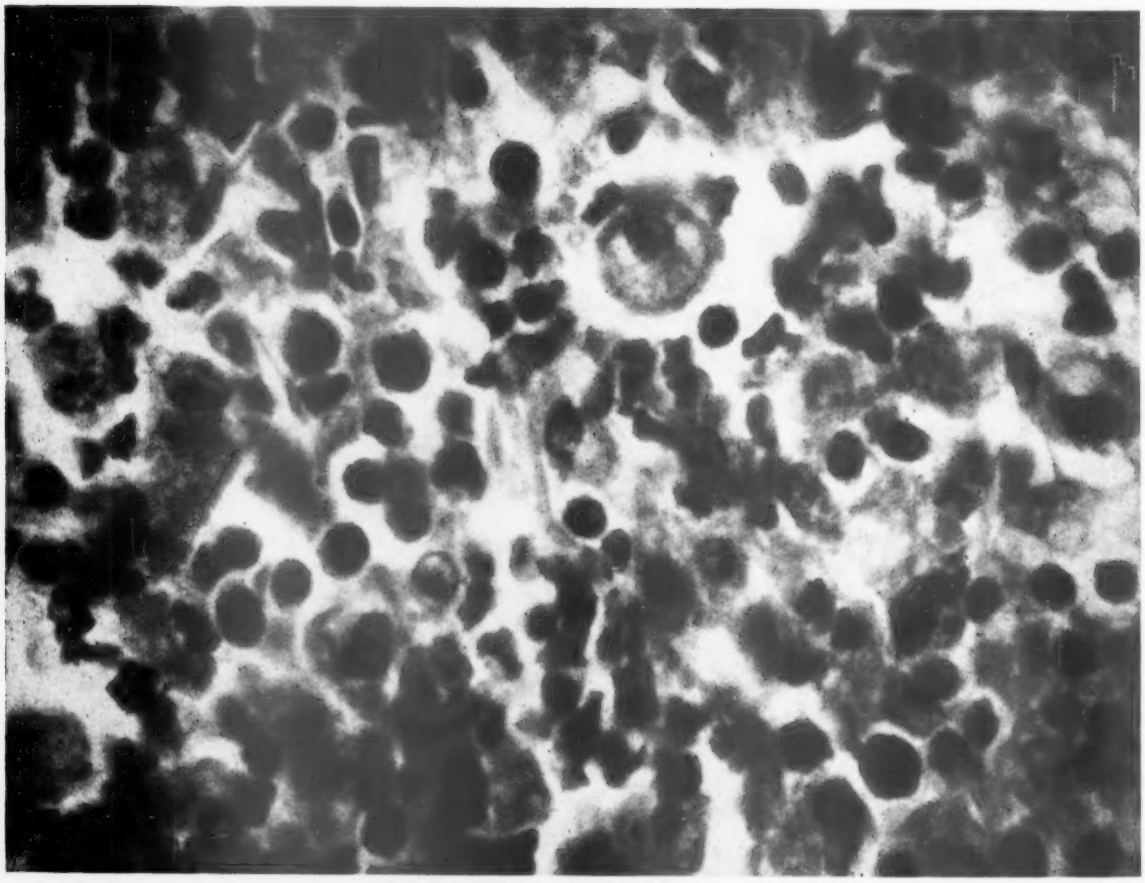

FIG. 2.—Spleen of Case 2 × 800.

number of haemohistiocytes were present in the peripheral blood. It is interesting to note that 6% atypical mononuclear cells were present in the blood of our case 1.

Claireaux and Lewis (1950) reported a case of non-lipoid reticulo-endotheliosis in a child of 14 weeks in which repeated marrow punctures yielded no material. This patient also had enlarged glands in the porta hepatis. In the case records of the Massachusetts General Hospital (1942) appeared the report of a girl aged 23 months with obstructive jaundice which at necropsy was found to be due to enlarged lymph nodes in the porta hepatis. The histology was typical of Letterer-Siwe disease.

Mallory (1942) discussing Letterer-Siwe disease and its possible relationship with Schüller-Christian disease and eosinophil granuloma of bone, stated that the proof of the relationship of these diseases must await the discovery of the aetiological agent. He regarded recent pathological studies as pointing strongly away from a fundamental metabolic disorder and towards a specific infectious agent. Siwe (1949) regarded non-lipoid reticulosis as a distinct disease on the grounds that its onset, course, and prognosis were different from both Schüller-Christian disease and eosinophil granuloma. While some cases of non-lipoid reticulosis appeared to be related to infection, he stressed the need to keep an open mind as to aetiological possibilities.

The cases we have reported favour an inherited rather than an environmental cause.

Summary

The cases of two sisters who died in early infancy with anaemia and hepato-splenomegaly are reported.

The clinical histories and histological appearances are characteristic of Letterer-Siwe disease.

Our thanks are due to Dr. C. W. Kesson and Dr. H. Spencer for permission to publish the cases, and to Professor T. Crawford for his advice and assistance in preparing the paper.

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AURICULAR SEPTAL DEFECT IN ONE OF MONOZYGOTIC TWINS

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 15, 1951)

In the cardiac clinic of the Hospital for Sick Children, Toronto, a 6-year-old girl with an auricular septal defect was found to have a monozygotic twin in whom the heart was normal.

Instances of congenital heart disease in both of monozygotic twins have been reported by several authors. Smith (1929) observed a patent ductus arteriosus in both of twin boys of similar general appearance, size, and weight. Ullrich (1938) described a case of congenital hypertrophy of the heart muscle in two members of a set of triplets that developed from two ova. The monozygotic pair were the affected ones, the third member being normal. Cor biloculare and persistent truncus arteriosus in both of twin brothers was found by Giustra and Tosti (1939). Pezzi and Carugati's cases (1924) of concordant dextrocardia with situs inversus in twin soldiers have been quoted by various authors as an instance of congenital heart disease in monozygotic twins, but the original article makes no reference to the zygosity of the twins.

On the other hand, congenital cardiac abnormalities in one member of a monozygotic twin pair have also been reported. Dubreuil-Chambardel (1927) observed monozygotic twins in France, only one of whom had dextrocardia and transposition of the viscera. In Germany Weitz (1936) noted patent ductus arteriosus also occurring in only one of a monozygotic pair. Rabl and Schulz (1940) erroneously report Dissmann's (1932) description of congenital aortic stenosis as appearing in one of uniovular twins. The original paper, however, describes these children as binovular twins. In the English literature we have been able to locate one case of discordance. A patent ductus arteriosus in one of twin girls is described by McClintock (1945). In her article there is an interesting history of identical twins on both the maternal and paternal sides of the family. However, the only evidence of monozygosity mentioned in her paper is that of a single placenta which is now known to be insufficient proof. To these instances of congenital heart disease

FIG. 1.—The twins (Deanna on the left and Donna on the right).

in one of identical twins, we should like to add the present report.

Case Report

The twins, Donna and Deanna, were born in Toronto on November 30, 1943, the only children of a mother aged 19 years at the time of delivery. There is no known family history of twinning on either side, nor of congenital defects. Both parents' blood tests were negative for syphilis. The mother was well during her pregnancy and did not suffer from any disease, such as German measles.

Evidence of Monozygosity. In physical appearance, the children are extremely alike, as may be seen from the accompanying photograph (Fig. 1). The affected twin (Deanna) is slightly smaller and lighter than her sister, being 44½ in. tall and 38½ lb. in weight, compared with Donna's height of 45¼ in. and weight of 40 lb. Both child is every bit as active as her twin. Both children have had chickenpox and measles. Deanna had infective hepatitis in 1949, at which time she was seen at the Hospital for Sick Children and the congenital heart lesion was first diagnosed.

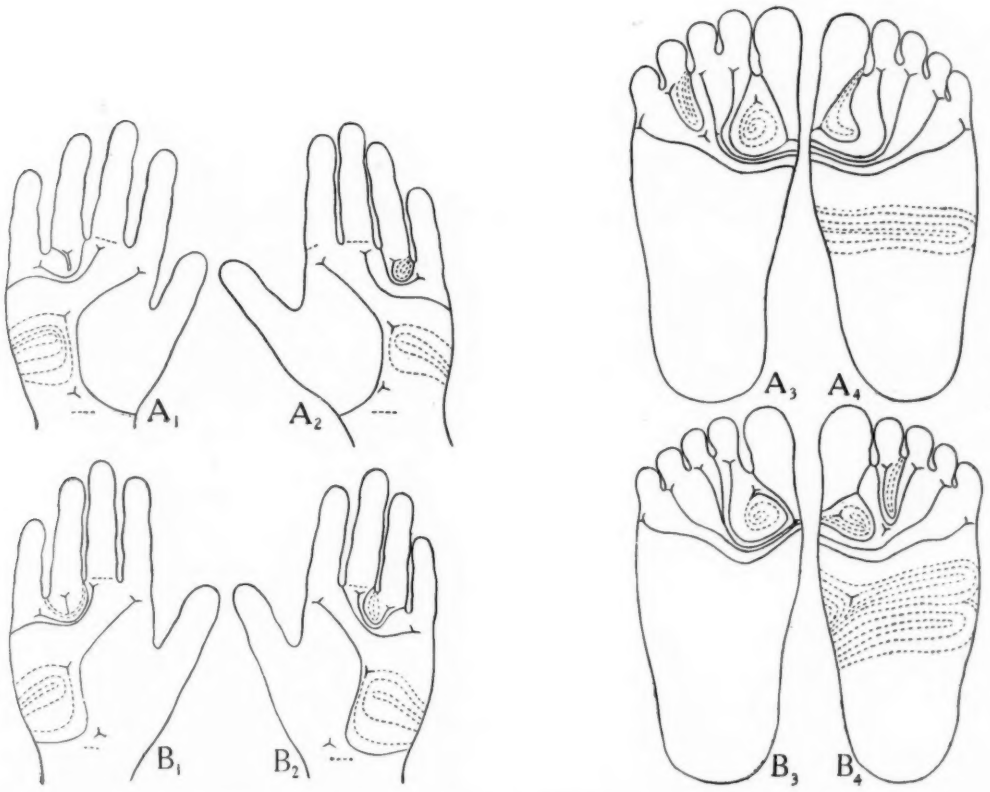

FIG. 2.—Prints of palms and soles of (A) Donna and (B) Deanna.

At birth, Donna, the first born, weighed 4 lb. 10½ oz. and Deanna, the patient, 3 lb. 11½ oz. There was a single placenta which was examined at the time of delivery by Dr. Ford Walker who injected it with liquid latex and recorded two chorions with two separate circulations. This type of placenta is now known to occur with fair frequency among monozygotic twins. In an extensive study now being conducted by Dr. Walker (1950) 27·5% of monozygotic twins have been recorded as dichorionic.

The children gained weight satisfactorily and passed the landmarks of development, such as sitting up, walking and talking, at the expected ages, the normal twin being about a month ahead of her sister. At present both children are attending school. The affected have a fair complexion, blonde hair, and blue eyes. The ears are very similar, and the teeth are alike in shape and occlusion. They show wide diastemata between the upper lateral incisors and cuspids. The children are both right-handed, and have in common a quiet, shy disposition. They are of normal intelligence.

The dermal configurations, which were printed by the Faurot technique and formulated according to standard methods (Cummins and Midlo, 1943), revealed similarities of the type found in monozygotic twins. The accompanying diagrams (Fig. 2) and formulations (Table 1) of the palms and soles illustrate the resemblances between Donna and Deanna. The homologous hands and feet of the twins are more nearly alike than the two hands or two feet of either one individual.

TABLE 1

DIGITAL, PALMAR, AND PLANTAR FORMULAE OF THE TWINS

DIGITAL PATTERNS AND RIDGE COUNTS

		Left Fingers 5	4	3	2	1	L.	Total	R.	Right Fingers 1	2	3	4	5
Donna	Patterns	L^u	L^u	L^u	L^u	L^u				L^u	W	L^u	L^u	L^u
	Ridge counts	0–12	0–14	0–3	0–9	0–16	54	132	78	17–0	14–14	14–0	18–0	15–0
Deanna	Patterns	L^u	L^u	L^u	L^u	L^u				L^u	L^r	L^u	L^u	L^u
	Ridge counts	0–12	0–13	0–12	0–16	0–14	67	139	72	19–0	0–15	12–0	14–0	12–0

PALMAR FORMULAE

	Left Palm Main Lines	Axial Triradii	Patterns	Right Palm Main Lines	Axial Triradii	Patterns
Donna	9 .7(X). 5″ .1	tt″	L^u.0.0.0.1(0)	9(8). 7(6). 5″ .1	tt″	L^u.0.0.0.L
Deanna	9(10). X .5″(6) .3	tt″	L^u.0.0.0. 0	11 .9(10).7(8) .3	tt″	L^u.0.0.L.0

PLANTAR FORMULAE

	Left Sole Main Lines	Patterns	Right Sole Main Lines	Patterns
Donna	15. 9.15 15 . 13	0.0.0.0/W.0.L_y.0	15.15 15. .15 . 13	0/L^t .0.0.0/L^d.0 .0.0
Deanna	15.15.14.15 hal. 11/10	0.0.0.0/W.0.0 .0	15.15.13(12) .11(10).15	L^t/L^t.0V.W/0^y.L^d.0.0

Symbols: L^u, loop ulnar; L^r, loop radial; W,whorl; X, abortive main line; t, axial triradius; L^d, loop distal; L^t, loop tibial; V, vestige of pattern; y, proximal triradius; hal, hallucal pattern.

TABLE 2

PERCENTAGE DIFFERENCE BETWEEN HANDS OF TWINS COMPARED WITH AVERAGES FOR MONOZYGOTIC AND DIZYGOTIC TWINS

	Ridge Counts of Fingers (%)	Types of Finger Patterns (%)	Main Lines and Axial Triradii (%)	Palmar Patterns (%)	Average Difference (%)
Donna and Deanna	15·2	10·0	28·4	25·0	19·7
Monozygotic* twins	10·9	23·0	17·6	21·4	15·9
Dizygotic twins	32·5	47·0	31·5	32·0	34·0

* Percentage differences for monozygotic and dizygotic twins are from unpublished data of Ford Walker.

Analysis of the digital and palmar configurations shows that the total difference of 19·7% between the pair follows the mean difference for monozygotic rather than for dizygotic twins (Table 2). The plantar formulae show slightly more variability (Table 3). The blood group

TABLE 3
PERCENTAGE DIFFERENCE BETWEEN SOLES OF TWINS COMPARED WITH AVERAGES FOR MONOZYGOTIC AND DIZYGOTIC TWINS

	Main Lines (%)	Plantar Patterns (%)
Donna and Deanna ..	45·0	28·6
Monozygotic twins ..	32·1	32·7
Dizygotic twins	66·0	62·5

studies are summarized in Table 4 and show complete concordance. All the evidence taken together, therefore, shows that Donna and Deanna are monozygotic twins.

TABLE 4
BLOOD GROUPINGS OF TWINS AND THEIR PARENTS

	Group	M and N Grouping	Rh Grouping
Donna ..	A_1	N	Negative cde/cde
Deanna ..	A_1	N	Negative cde/cde
Father ..	A_1	MN	Positive cDE
Mother ..	O	MN	Negative cde/cde

The Heart Lesion. Deanna has an auricular septal defect. There is no cyanosis or clubbing of the fingers. The femoral arteries are palpable and the blood pressure 110/60 mm. Hg. The apex beat is in the fifth space inside the mid-clavicular line. On palpation, the heart beat is forceful, but no thrill is detectable. There is a moderately loud, blowing, systolic murmur of moderate duration heard maximally in the pulmonary area, but detected also all over the praecordium and posteriorly between the scapulae. There is an accentuated second pulmonary sound. Fluoroscopic examination reveals moderate cardiac enlargement, the ratio of the transverse diameter of the heart to the internal diameter of the chest being 10·0 cm.:18·5 cm. The enlargement affects both ventricles and, in addition, there is bulging of the pulmonary conus. The hilar shadows are of increased density and are actively pulsatile. The radiograph is reproduced in Fig. 3 together with that of Donna. Right axis deviation is seen only in Deanna's electrocardiogram (Fig. 4), her sister's being normal. The results of cardiac catheterization for the affected child are seen in Table 5. The rise of oxygen content in the right auricle is significant, and anatomical proof of auricular septal defect was furnished by the entry of the tip of the catheter into the left auricle and then into a pulmonary vein. The pressure readings in the various chambers were within normal limits.

TABLE 5
RESULTS OF CARDIAC CATHETERIZATION OF DEANNA

Situation of Catheter	Oxygen Content Vol. %
Superior vena cava	9·54
Right auricle	12·00
Right ventricle	12·03
Right pulmonary artery ..	11·91
Left auricle	13·11 (88% saturated)

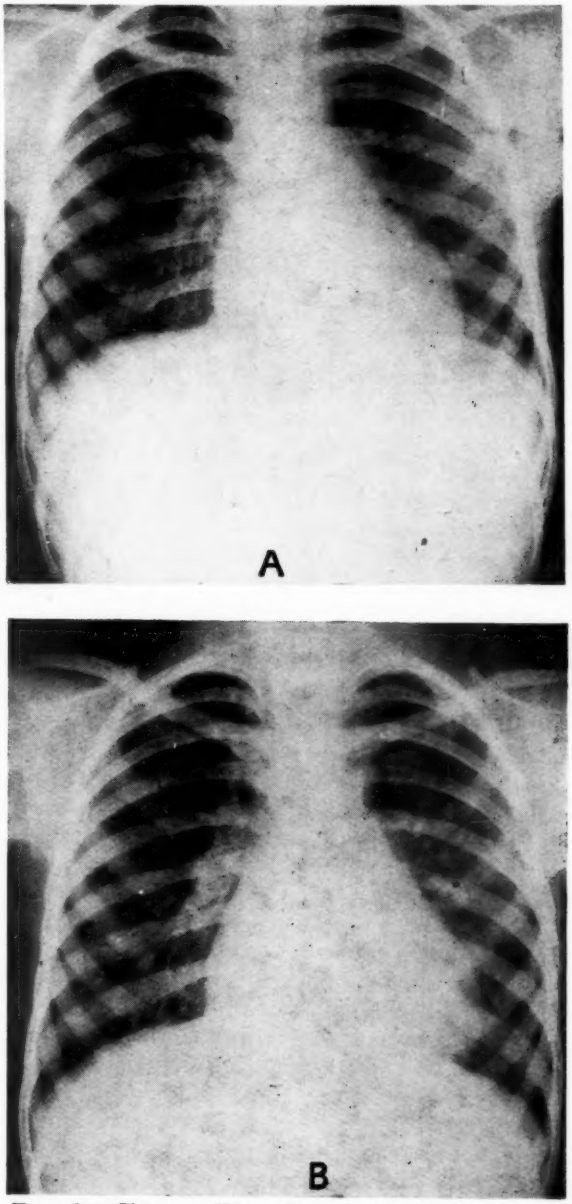

FIG. 3.—Chest radiographs of (A) Donna and (B) Deanna.

Physical examination and fluoroscopy, radiographs and electrocardiography revealed no abnormality in Donna. Cardiac catheterization was not carried out on this child.

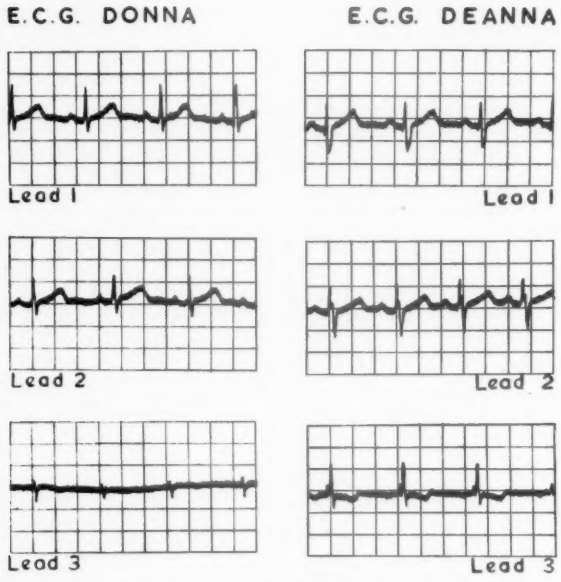

FIG. 4.—Electrocardiograms of the twins.

Discussion

It was once thought that one of homologous twins never suffered from a malformation not shared by his fellow (McFarland and Meade, 1932). If, therefore, a pair of twins did not show identical abnormalities they were classified as dizygotic. Such interpretations ignored the fact, now accepted, that environment may modify a given hereditary trait. A congenital malformation may result from an error in development, such as an abnormality in the rate of growth or differentiation of the embryo, at some specific time. Muller (1947) points out that the characteristic expression of a given gene complex requires specific environmental conditions.

The possible causes of a congenital malformation are thought to be a genetic defect in the fertilized ovum or a faulty intrauterine environment. To these Dahlberg (1949) suggests that a third factor, ' random variation,' be added, which occurs within the developing embryonic cells.

In certain instances of congenital heart disease, a hereditary trait is apparent. In the present study there is nothing relevant in the family history. Monozygotic twins make a unique contribution to aetiological research as, in respect of their genetic constitution, they are one and the same individual in duplicate. It follows, therefore, that any discordance they may exhibit must be a reflection of differences in their experience subsequent to the twinning division. When one member of a monozygotic pair presents a particular abnormality not shared by his fellow, it is safe to conclude that the cause of the discordance is not genetic.

Of non-hereditary factors resulting in malformation of the embryo, maternal disease is the most obvious. Syphilis and a virus infection during pregnancy have been proved to cause congenital defects in the offspring. It is well known that German measles occurring in the first two months of pregnancy is associated with a high incidence of congenital heart disease. In the present case the mother was in good health throughout her pregnancy.

Twins show a higher incidence of prematurity and stillbirths than singletons (Strandskov and Ondina, 1947). It is a common observation also that congenital abnormalities occur more frequently among multiple pregnancies. In the case of twins the unfavourable factor may act on one of the developing foetuses to produce a malformation or, in some cases, to cause even the death of one twin. The survival of only one member of a monozygotic pair is a well recognized occurrence, and must reflect a difference in uterine environment. The quality of the latter is poorer in women when more than one baby is produced. In the later months of pregnancy crowding and an abnormal intra-uterine position may be injurious to the foetus. However, crowding is minimal during the second month of intra-uterine development, at which time the auricular septum is formed, and it is unlikely to have any bearing upon the present case.

In the monozygotic twins under discussion there was a single placenta with two chorions and two separate circulations. A pressure abnormality in one system, occurring at the time of closure of the auricular septum, might have been the cause of the congenital malformation in only one twin.

An abnormal change in temperature or in *p*H within the cells of an embryo in the early stages of development may lead to congenital defects. This random variation might have affected one embryo and not the other, leading to the different expression of the same gene complex in the present monozygotic pair.

Summary

Auricular septal defect is reported in one of monozygotic twin girls, aged 6 years, her twin being clinically normal. The analysis of zygosity is based upon consideration of the foetal membranes, the blood groups and types, the digital, palmar, and plantar configurations and other physical features.

The two individuals came to differ in their characterization because of a variation in their experience subsequent to conception, such as differences in their circulation in early pregnancy or some random physico-chemical variation in their embryonic development.

We wish to thank Dr. John D. Keith of the Hospital for Sick Children, Toronto, Dr. Norma Ford Walker of the Department of Zoology, University of Toronto, and Professor F. A. E. Crew, of the Department of Public Health and Social Medicine, University of Edinburgh, for their help and encouragement in the preparation of this paper. We are indebted to Dr. Beatrice M. Corrigan for her translation of the article by Pezzi and Carugati (1924).

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INCLUSION DISEASE IN CHILDHOOD

BY

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It is well established that many viruses produce inclusion bodies in the nucleus or cytoplasm of an affected cell, and that the morphological appearance of such inclusions may be pathognomonic of a particular infection (Pinkerton, 1950). Similar bodies may also result from the toxic action of certain heavy metals (Lee, 1933; Blackman, 1936; Olitsky and Harford, 1937). They are occasionally found in cirrhotic livers, and Russell bodies are frequent in many non-specific inflammatory lesions. In view of these facts, Cowdry, Lucas, and Fox (1935) stated that the finding of inclusion bodies should be accepted with caution as evidence of viral infection. When they are conspicuous without the aid of oil immersion microscopy, are focal in distribution, and are related to marked lesions in the surrounding tissue, it is probable that they indicate a viral infection.

Intranuclear inclusions are divided into two types (Cowdry, 1934). Type A inclusion bodies are represented by a mass of eosinophilic material in the centre of the nucleus with collections of basophilic substance near the nuclear membrane. Complete disintegration of the cell ultimately occurs, and such cells are accompanied by a noticeable reaction in the surrounding tissues. This variety is seen in herpes, yellow fever, varicella, etc. Type B inclusions show a similar acidophilic accumulation in the nucleus which pushes the other nuclear components towards the nuclear membrane. There is no extensive destruction and no severe tissue reaction. Both types, and particularly type B, have been found in a number of apparently healthy animals of various species (Cowdry *et al.*, 1935).

In 1920 Jackson observed inclusion bodies in the salivary glands of guinea-pigs. The affected cells were greatly enlarged and contained type A intranuclear inclusions and numerous small intracytoplasmic inclusion bodies. Cole and Kuttner (1926) first isolated a virus from affected guinea-pigs and, since then, the association of the salivary gland virus with the morphologically distinct inclusion cells has been firmly established (Markham, 1938, Rosenbusch and Lucas, 1939). Identical cells have been discovered in rats (Thompson, 1932), mice (Thompson, 1934), monkeys (Cowdry and Scott, 1935a and b), and mole (Rector and Rector, 1934). Efforts to transfer the infection from one species to another have failed, and it is now recognized that the virus is strictly species specific (Kuttner and Wang, 1934).

Occasional reports of peculiar cells in human organs, almost invariably in infants and young children, have appeared in the literature since they were first described by Jesionek and Kiolemenoglou in 1904. These were regarded as representing protozoa until Goodpasture and Talbot (1921) recognized their similarity to the bodies described in the lesions of vaccinia (Tyzzer, 1906) and in the salivary glands of guinea-pigs (Jackson, 1920). It was later observed that these cells had the same morphology as those found in animals infected with a salivary gland virus. So far, however, attempts to isolate a virus from human material have failed (Kuttner and Wang, 1934). All affected cells are enlarged to a diameter of 20-40μ so that they are two to four times as large as unaffected cells (Fig. 1). Most authors point out that transitions from normal to abnormal cells are rarely if ever seen, although stages in the development of the inclusion bodies have been described (Cappell and McFarlane, 1947). Often there is a condensation of the cytoplasm to form a thick refractile cell membrane, a feature most prominent in those cells showing evidence of degeneration.

The intranuclear inclusion bodies are two to three times as large as normal unaffected nuclei. Although usually round or oval, they may be reniform or distorted into bizarre shapes. They are acidophilic and often homogeneous, although sometimes they appear to be composed of numerous tiny particles.

A clear halo invariably separates the inclusion from the nuclear membrane on which are small

condensations of chromatin (' orbital bodies '). One of these is normally considerably larger than the others and, when the inclusion body is reniform, this chief orbital body lies opposite the indentation. While one inclusion in each nucleus is the rule, two or more may be present. There is usually a single body in each nucleus in multinucleated cells.

Compared with the intranuclear inclusions, those in the cytoplasm are of restricted incidence, and appear only when the former are well developed (Pearson, 1930). They are numerous, round or oval and basophilic, and lie in the cytoplasm towards the unattached margin of the cell, sometimes forming regular rows. The overlying double-contoured cell membrane may be thinned, and the cytoplasm may bulge and produce an acorn-shaped cell (Cappell and McFarlane, 1947). Vacuolation of the cytoplasm is frequent.

Animals infected with a salivary gland virus exhibit no signs of disease. Many instances have now been described of human cases in which isolated lesions of a similar type were found in single organs at necropsy. In the majority sufficient cause for death was found, and there was no suggestion that a virus disease had caused symptoms or had affected the course of the primary disease. In 23 cases, however, lesions were present in many organs and, in some of these, there was no co-existing disease.

The purpose of this paper is to report four cases of generalized inclusion disease, to summarize six cases where lesions were found in one or two organs only, and to attempt to elucidate the clinical features of the disease as it occurs in children.

Case Reports

Case 1. P.G., a white British girl, aged 4 months, was the first child of healthy parents. The Wassermann and Kahn reactions of the mother's blood were negative. The infant was delivered normally at term, weighing 2,950 g. When 3 days old she developed jaundice which became very intense and then diminished slightly. During the first 18 days of life she passed only three stools all of which were black. The umbilical cord separated on the seventh day, but the umbilicus continued to bleed slightly. A purulent nasal discharge began at the age of 14 days.

When 18 days old, the patient weighed 2,440 g., and was wasted and apathetic. Her temperature was subnormal (95-96° F.) and her pulse slow (92-120 per minute). The forehead was deeply wrinkled. The isthmus of the thyroid was palpable. Generalized jaundice was marked, and the liver edge was palpable 2 cm. below the right costal margin. The spleen could not be felt. Although the umbilicus bled easily, there was no obvious omphalitis.

LABORATORY INVESTIGATIONS. When the patient was 18 days old, laboratory investigations were made and gave the following results: Hb. 120%; R.B.Cs., 6 million per c.mm.; W.B.Cs., 7,000 per c.mm. (polymorphs, 52%, lymphocytes, 26%).

The mother's blood group was A Rh positive (Anti-C +, Anti-D +, Anti-E −), and the child's, Group A Rh positive (Anti-C +, Anti-D +, Anti-E −).

The urine contained no bile. The direct Van den Bergh reaction was negative, and the indirect weakly positive. Culture from the umbilicus produced a scanty growth of *Staphylococcus aureus* (coagulase positive). The serum cholesterol level was 212 mg. %.

COURSE. Test feeding on admission to hospital showed that the mother had a poor supply of breast milk and complementary feeding was started. The jaundice gradually diminished, and had completely cleared by the age of 31 days. Regular daily motions began and, with a caloric intake of 132 calories per kg. body weight, the infant regained her birth weight at 46 days. She remained difficult to feed, never opened her eyes, and was extremely lethargic. At 9 weeks, the child was clinically an unmistakable cretin with an umbilical hernia, and marked supraclavicular and axillary pads. A radiograph of the skull and long bones showed marked immaturity with retardation of osseous development. An electrocardiogram revealed slight S-T deviation in lead 2 and low voltage P-T waves, most marked in lead 1. The serum cholesterol level was 186 mg. %. At this time treatment with thyroid extract was begun (grain $\frac{1}{8}$ b.d., gradually increasing to grain $\frac{1}{4}$ t.d.s.).

After 11 days' treatment there was a great change in the infant, who now weighed 3,520 g. and had a normal temperature and a pulse rate of 120-130 per minute. She fed well and motions became regular. Good progress was made until four weeks after thyroid therapy was begun when pyrexia, diarrhoea, and vomiting appeared. Thyroid extract was discontinued; she was given glucose-saline by mouth only, and penicillin therapy was started. Three days later dehydration developed, and intravenous fluids were given. The stools became very pale, and jaundice and slight hepatomegaly were noted. By the twelfth day of this acute episode she was deeply jaundiced, the stools were white, and the urine deeply bile-stained. The liver extended to the umbilicus. Three days later, however, all signs rapidly disappeared, and the liver became barely palpable. Thyroid extract was given again. She remained well for only six days when there was a recurrence of diarrhoea, abdominal distension, and dehydration. Despite intravenous therapy and a small blood transfusion, her condition rapidly deteriorated, and she died after 11 days of acute illness.

NECROPSY FINDINGS. There was generalized jaundice over the whole body, with evidence of moderate loss of weight.

Both lungs were well expanded and showed no evidence of disease.

The spleen (10 g.) was firm. Its cut surface was a homogeneous light brown with indistinct Malpighian bodies. An intense Prussian blue was produced when it was treated with potassium ferrocyanide and dilute hydrochloric acid.

The liver (162 g.) was greenish-brown on both its external and cut surfaces. The lobular pattern was

indistinct. The gall bladder contained a little dark green bile and the hepatic and common bile ducts were patent.

Both kidneys (right, 20 g.; left, 21 g.) appeared normal.

The thyroid gland (3·4 g.) was of normal size and appearance.

Apart from a minor degree of bile-staining of all organs, no other abnormalities were found.

MICROSCOPY. The general architecture of the thyroid (Fig. 2) was distinctly abnormal. In most places it was difficult to distinguish an acinar arrangement, the secretory cells having apparently proliferated and obliterated the lumina. The cells varied in size and shape, most having an irregular outline. The nuclei tended to be round or oval with a vesicular chromatin network, but often they were crenated and possessed denser chromatin. The cytoplasm was faintly eosinophilic and many of the larger cells showed small vacuoles. Where acini could be distinguished they were lined by irregular, vacuolated cells. The lumen often contained a few desquamated cells, but no colloid. Scattered throughout the gland were many large cells in various stages of degeneration and showing inclusions in their nuclei. The typical arrangement of the chromatin into beads was frequently lacking. Intracytoplasmic granules were absent, the cytoplasm often being occupied by numerous small vacuoles. Inclusion cells were found both singly and in groups of up to about 30. When isolated, they lay either in the walls of acini or amongst proliferated secretory cells, and they showed no associated inflammatory reaction. When in groups it was often impossible to determine whether they lay in secretory tissue or in interstitial tissue. Such collections were surrounded by varying numbers of lymphocytes and plasma cells which extended locally into the adjacent interstitial tissue. Nowhere was there any evidence of fibrosis.

The general architecture of the liver was normal. The majority of the hepatic cells throughout the lobule contained small granules of haemosiderin. A few cells showed moderate fatty change, and some possessed two or three nuclei. There were many bile plugs in dilated canaliculi. The portal tracts were generally normal, but here and there inclusion cells completely occluded the lumina of the small bile ducts. They were invariably single, and were less degenerate than those in the thyroid. Intracytoplasmic inclusions were generally absent.

A few inclusion cells, occurring singly or in pairs, were present in the tubules of the renal cortex, lying between normal cells and projecting into the lumen which was never dilated. Intracytoplasmic granules were prominent. There was no inflammatory reaction.

Except for occasional inclusion cells within the acini, the pancreas was normal.

Several isolated inclusion cells were found in the alveoli of the lungs, where they were apparently attached to the alveolar walls. Throughout both lungs, many of the alveoli contained mononuclear cells.

Several degenerate inclusion cells were present in the anterior pituitary. They occurred singly and produced no inflammatory response.

Both the submaxillary salivary glands showed numerous inclusion cells, mainly in the small ducts where several were frequently adjacent. A few were present in the acini. All were degenerate, and surrounded by a well marked inflammatory exudate in the interstitial tissue. This consisted mainly of lymphocytes and plasma cells. Cytoplasmic granules were evident in the majority of the inclusion cells.

In the spleen there was a considerable increase in the number of reticulo-endothelial cells in the pulp, almost all of which contained coarse granules of haemosiderin.

No abnormalities were noted in any other organ.

The main lesions were cretinism (clinical); enteritis (clinical); and inclusion cells in thyroid, salivary gland, liver, kidney, lung, pancreas, and pituitary.

Case 2. D.S., a white American girl, aged 14 days, was born of healthy parents by breech delivery without instruments after a labour lasting four or five hours. The infant was slightly icteric at birth, and small red spots were present over the whole body. Her birth weight was 2,320 g.

A physical examination was made on the fifth day. The child weighed 2,240 g., and was 44 cm. long. She was very small, particularly her head which was 29 cm. in circumference. Generalized purpuric lesions and jaundice of the skin were noted. Small, hard lymph nodes were palpable in the cervical, axillary, and inguinal regions. The liver edge was 5 cm. below the right costal margin, and the spleen 4 cm. below the left costal margin. There was a fine tremor of the arms when the infant cried. All other systems were normal.

LABORATORY INVESTIGATIONS. On the sixth day a blood examination gave Hb. 10·9 g. %; R.B.C.s 2·9 million per c.mm.; platelets 16,000 per c.mm.; W.B.C.s 6,200 per c.mm. (polymorphs, 26%, lymphocytes, 66%; monocytes, 4%; eosinophils, 2%; basophils, 2%). The coagulation time was 4½ minutes, and the bleeding time 4½ minutes. The infant's blood was Rh positive. On the seventh day the platelets were 10,000 per 100 W.B.C.s.

Examination of the urine on the sixth day gave albumin +++, bile +, W.B.C.s 4-6 per high power field. Many micro-organisms were seen; 2-4 leucocytic, granular, and mixed hyaline casts per high power field. On the tenth day an occasional white cell was present, 0–4 granular and hyaline casts per high power field.

The blood culture on the fifth day showed no growth.

The cerebrospinal fluid on the seventh day showed protein 146 mg. %, sugar 35 mg. %, chlorides 722 mg. %. On culture *Staphylococcus albus* (coagulase negative) was isolated. On the tenth day the C.S.F. was clear and xanthochromic.

A radiograph was taken on the sixth day and showed that the sutures of the skull were widely separated with diffuse calcification involving both parietal regions of the brain. The findings were considered to be typical of toxoplasmosis.

Transfusions of 30 ml. of whole citrated blood were given on the seventh and eleventh days without improvement.

When seven days old, the baby had several convulsive attacks consisting of clonic jerks and twitchings of both

arms. Her respirations finally became laboured and during the last three days the temperature fell to the region of 94° F.

NECROPSY FINDINGS. The body was mildly jaundiced, and moderately emaciated.

Both lungs were well expanded with small areas of emphysema.

The liver (123 g.) had a smooth, dark, brownish-green capsule mottled by deeper red areas. It was moderately firm. The cut surface was brownish-green and showed normal lobular markings. The gall bladder contained dark green bile.

The pancreas and spleen (35 g.) appeared normal.

The thymus (1 g.) showed a poorly defined lobular pattern. Small punctate haemorrhages were present beneath the pleura and pericardium and into the mucosa of the ileum and bladder. Apart from generalized bile-staining all other viscera were normal.

The brain was small with a normal gyral pattern, obscured in places by a greyish yellow discoloration of the leptomeninges. Two such areas were present over the left temporal and right central regions measuring 1·2 and 0·6 cm. in diameter respectively. The cortex beneath these areas showed punctate yellow discoloration and a number of tiny haemorrhages. There was a slightly protuberant, poorly defined area of increased density about 0·8 cm. in diameter in the anterior portion of the right temporal lobe. On section the lateral ventricles were of normal size. There were linear, serrated bands of dull, yellowish white tissue in the cortex of many of the gyri in the frontal, temporal, and parietal lobes. In some places this abnormal layer was punctate due to the interposition of semi-translucent, greyish tissue between the yellowish areas. Similar lesions were present beneath the ependyma of both lateral ventricles, and a few yellowish areas up to 1 mm. in diameter were seen in the left basal ganglia and the left thalamus. The cerebellum, brain stem, and spinal cord showed no gross abnormalities.

MICROSCOPY. The majority of the alveoli of the lungs contained granular material, red blood cells, cornified amniotic cells, large vacuolated mononuclear cells, and many bacteria. Similar elements were in the bronchi and bronchioles. A few alveolar ducts were dilated and lined by hyaline membrane. There were occasional typical inclusion cells in the alveoli, the majority of which lay alongside the wall to which they appeared to be attached; others lay freely in the alveolar spaces.

The normal architecture of the liver was distorted by an increased amount of connective tissue in the portal areas and between the hepatic cords in some lobules. Many newly formed bile ducts contained plugs of bile, and there were granules of haemosiderin both in liver cells and in the swollen Kupffer cells. There were many foci of haemopoiesis. Only in the smaller bile ducts were inclusion cells seen, and in several places it appeared that they completely obstructed the flow of bile.

A number of acini in the pancreas were distended by an eosinophilic secretion with flattening of the acinar cells. Between the acini there was increased connective tissue in which there were moderate numbers of myeloid cells. Scattered inclusion cells lay in acini and the islets of Langerhans (Fig. 3).

Many of the convoluted tubules of the kidney contained inclusion cells, as many as 20 being present in the cross section of a single tubule. The majority of the affected tubules were considerably dilated, and often surrounded by a lymphocytic infiltration into the interstitial tissue. The affected tubules were mainly in the outer half of the cortex. There were small foci of haemopoiesis in the tissues surrounding the pelvis.

In the thyroid occasional colloid-filled acini contained a single inclusion cell, and here and there collections of typical cells completely obliterated the lumen.

The thymus showed accidental involution.

The pulp of the spleen contained many small foci of haemopoiesis without any obvious deposit of haemosiderin.

Large areas of the cortex of the brain were destroyed to form sharply defined, irregular zones in which there were innumerable basophilic granules either within degenerate nerve cells or forming round clusters. The arrangement of the nerve cells in the surrounding tissue was disturbed by mild astrocytosis. Calcified zones were present in the underlying white matter where there were occasional large plates of calcium in the corpus striatum and in the subependymal tissue. Many small collections of marginal cells were found in the region of the aqueduct and in one corpus quadrigeminum. The remainder of the brain stem and the spinal cord were normal.

The main lesions were calcification of brain with microcephaly; cirrhosis of the liver; cystic fibrosis of the pancreas; and inclusion cells in the lungs, liver, pancreas, kidney, and thyroid.

Case 3. D.G., a coloured American girl, aged 85 days, was born prematurely after a spontaneous delivery. The birth weight was 1,070 g. She was well until she was 72 days old when the labia became swollen and tender, and a reducible hernia in the left groin was noted. This remained visible for ten days when it began to disappear. Four days later snuffles began accompanied by swelling of the left thigh.

On the 77th day, a physical examination showed that the sternum retracted on inspiration, and a faint cry was emitted on expiration. There was a small umbilical hernia. Both liver and spleen were palpable 1·5 cm. below the costal margins. The vulva, perineum, and buttocks were reddened and oedematous. There was a firm swelling, 4 cm. in diameter, over the upper lateral aspect of the left thigh. Although it appeared to be tender it caused no limitation of movement. Dactylitis was seen in both hands.

LABORATORY INVESTIGATIONS. A blood count gave the following: Hb. 65%, R.B.C.s 3·41 m. per c.mm., W.B.C.s 10,000 per c.mm. (polymorphs, 78; lymphocytes, 19; myelocytes, 2; myeloblasts, 1). There were hypochromia and anisocytosis and less than one normoblast per 100 W.B.C.s. The urine showed a trace of albumin only. Vaginal and throat cultures revealed no pathogens. Blood culture was negative. The Kahn test was ++.

The general and local conditions remained about the same until the infant was 82 days old, when stridor

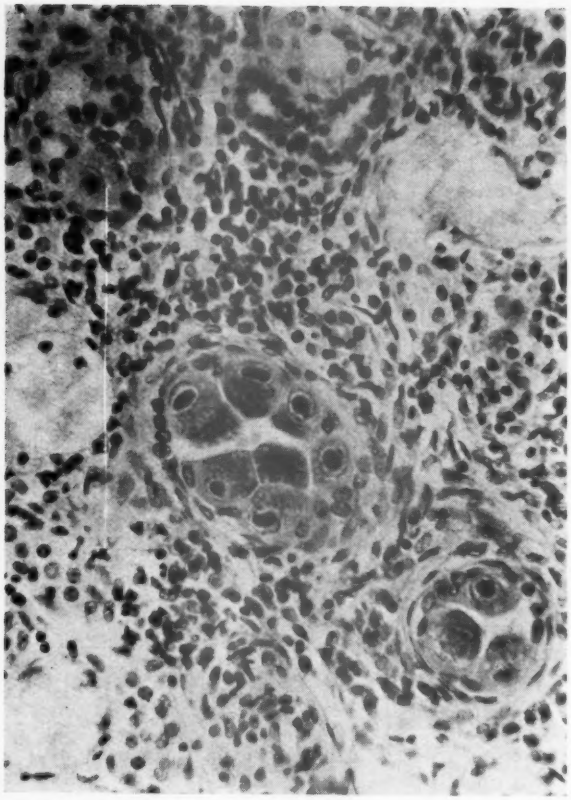

FIG. 1.—Typical inclusion cells in renal tubules of Case 2 (× 280).

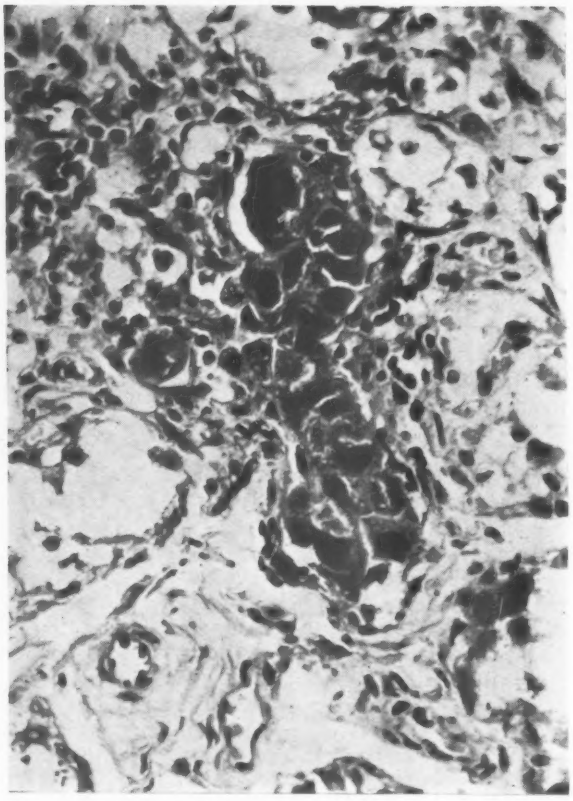

FIG. 2.—Thyroid gland of Case 1 showing collections of degenerating inclusion cells (× 380).

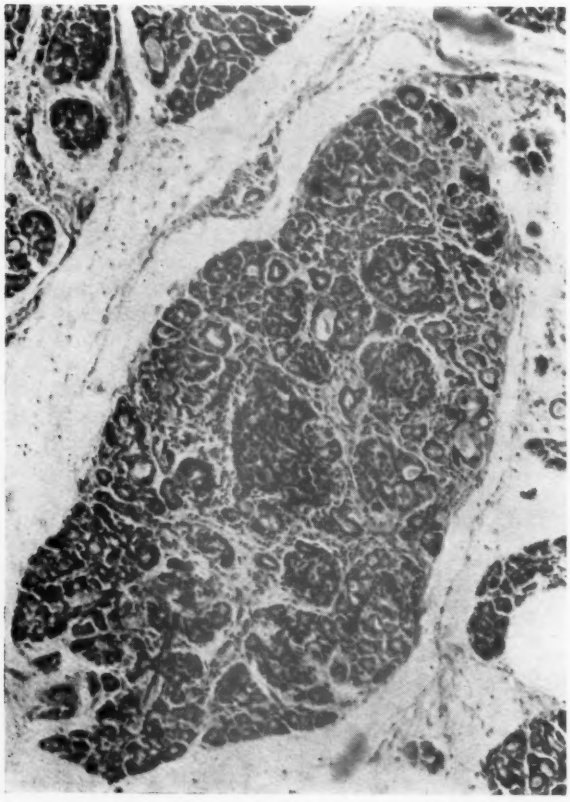

FIG. 3.—Pancreas of Case 2 showing mild cystic fibrosis with scattered inclusion cells (× 89).

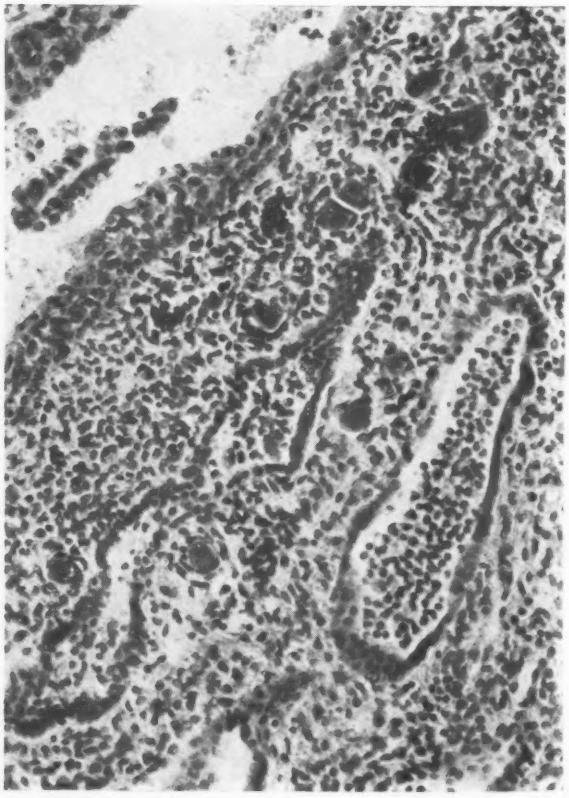

FIG. 4.—Kidney of Case 4 showing inclusion cells associated with collecting tubules and ascending pyelonephritis (× 175).

increased and there was marked depression of the sternum. The swelling of the buttocks and perineum lessened. An x-ray examination of the chest showed perihilar bronchopneumonia with emphysema of the left lung. The child rapidly became exhausted and died.

NECROPSY FINDINGS. The body was emaciated with a definite icteric tinge to the skin. There was a firm swelling of the upper half of the left thigh, and swellings of the middle phalanges of the right index and left middle fingers.

The lungs showed patches of emphysema anteriorly in all lobes.

The spleen (16 g.) had a soft, congested surface.

The liver (145 g.) was firm and brown with a greenish tinge. The cut section was even.

The gall bladder was rudimentary and contained a small amount of thick, dark green bile.

Both kidneys (right, 7·5 g.; left, 8·0 g.) appeared normal. The muscles attached to the upper end of the left femur were pale and of a yellowish-tan, and stripped readily from the underlying bone. The femur fractured transversely at a point just below its neck where the cortex was thickened. Here the marrow was pale and tough, resembling granulation tissue. Just above the irregular epiphyseal line at the lower end of the femur was a soft white area measuring 4 × 3 mm. The lower ribs on both sides were beaded and on section showed irregular epiphyseal lines.

A small amount of clotted blood lay over the left hemisphere of the brain.

All the other organs were of normal size and appearance.

MICROSCOPY. Many liver cells contained fat droplets, and in the region of the portal tracts occasional multinucleated cells were seen. Numerous foci of haemopoiesis were scattered throughout. There was a slight increase of connective tissue in the portal areas. No bile plugs or iron pigment could be demonstrated. In one portal area six typical inclusion cells completely blocked the lumen of a medium sized bile duct.

The general architecture of the pancreas was normal but occasional inclusion cells were seen in the acini.

In the lungs the alveoli contained large mononuclear cells in great numbers. Attached to the wall of one alveolus were several inclusion cells.

Large numbers of inclusion cells were present in the cortex of the kidneys, mainly in the outer half. They formed part of the epithelium of many of the convoluted tubules, as many as 30 being present in the cross section of a single tubule. Many affected tubules were considerably dilated, and some of these contained pink homogeneous material. Large areas of cellular infiltration were related to collections of inclusion cells. These consisted of lymphocytes, plasma cells, and occasional mononuclear cells. A few glomeruli showed capsular thickening but none was completely fibrosed.

In the periosteum of the upper end of the femur there were numerous polymorphs. The overlying muscle was oedematous, but showed no inflammatory infiltration. The marrow at both ends of the femur and in the upper end of the tibia was replaced by areas of granulation tissue.

Phalanges from both affected fingers showed granulation tissue, bone degeneration, and irregularity of the epiphyseal lines typical of syphilitic dactylitis. The spleen appeared normal and contained no haemosiderin. A single inclusion cell was found in a parathyroid gland. All other organs were normal.

The main lesions were congenital syphilis; acute osteomyelitis; and inclusion cells in liver, pancreas, lung, kidney, parathyroid.

Case 4. M.S., a coloured American girl, aged 57 days, was born after seven months' gestation. Birth was normal, and the child weighed 2,220 g. She was breast-fed for two and a half weeks and then artificially fed. Constipation was marked from birth, the stools being hard and bright yellow or green. During the week before admission to hospital at the age of 50 days she developed a cold with a skin rash.

Emaciation was marked, and icterus of the skin and sclera was evident. The liver was palpable 3 cm. below the right costal margin. No other abnormalities were found, and a diagnosis of a bile duct anomaly was considered.

During her seven days in hospital the baby took fluids poorly, vomiting two to three times daily after feeds. Bile was present in the stools.

The van den Bergh reaction was ++++ (biphasic), and the benzidine test on the urine was positive. Many clumped white cells were found in the urine. The Kahn test was negative. The temperature became subnormal and respirations laboured with an expiratory grunt for several days before death.

NECROPSY FINDINGS. The body showed evidence of considerable loss of weight and moderate generalized icterus.

The lungs showed marked emphysema of the anterior parts only, with increased consistency of the right lower lobe.

The liver (80 g.) was dark green, but had normal markings. The common, cystic, and hepatic ducts were explored and found to be patent.

Both kidneys (right, 13 g.; left, 12 g.) were mildly swollen, and the entire surface was mottled with yellowish-grey, opaque areas measuring 1-10 mm. in diameter. On section, these areas extended deeply into the cortex and in some places into the medulla. The boundary between the cortex and the medulla was blurred. All other organs appeared normal.

MICROSCOPY. The spleen showed increased cellularity of the pulp and marked haemosiderosis. With the exception of numerous granules of haemosiderin in most of the cells, the liver cords were normal. Bile plugs were present in some canaliculi. The Kupffer cells were enlarged and contained haemosiderin. The portal tracts were relatively cellular and showed no evidence of fibrosis. Several typical inclusion cells were present in the region of the portal tracts, but it was not possible to demonstrate their exact location in the bile ducts.

Triangular areas in the kidneys extended from the capsule to the pelvis. In these areas there was an extensive infiltration of polymorphs which almost obliterated the normal architecture. The tubules were filled with leucocytes, and their epithelium flattened,

whilst there was a polymorphonuclear and lymphocytic infiltration of the interstitial tissue, forming, in some regions, definite abscesses. Inclusion cells were present in the distal parts of some of the collecting tubules in the region of the pelvis. Occasional inclusion cells were surrounded by a mild infiltration of lymphocytes and polymorphs (Fig. 4). No typical cells were present in the cortex.

The alveolar walls of the lung were generally markedly thickened and infiltrated with lymphocytes, plasma cells, and mononuclears. In a few alveoli typical inclusion cells were present, some being attached to the alveolar wall.

The bronchi contained cellular exudate but the epithelial lining was generally well preserved. In the peribronchial regions, however, there was an infiltration of lymphocytes and plasma cells.

The main lesions were ascending pyelonephritis; interstitial pneumonia; and inclusion cells in liver, kidneys, and lungs.

Summary of Cases with Minimal Lesions

The clinical and pathological findings of six cases in which scanty inclusion cells were found in one or two organs are summarized in Table 1. Only one of the children was over 7 months of age. It is doubtful if infection by the salivary gland virus seriously affected the course of the primary disease in any case, although the possibility that it predisposed the infants to other infections cannot be ruled out. In Case 5 there was haemosiderosis of the liver which may have been due to the virus infection. The duodenal ulcers found in Case 7 were small superficial erosions of the first part of the duodenum. Many inclusion cells were found in the stroma, often close to capillaries, while others were located amongst epithelial cells, especially in Brunner's glands. The presence of inclusion cells in small numbers in many different organs, in the absence of gross pathological changes, emphasizes the fact that this infection is not uncommon, and that in the majority of cases it has little or no bearing on the clinical picture.

Discussion

Cases of Generalized Disease. From a study of the literature and from the cases described here the subject will be discussed under specific headings.

AGE AND SEX. Of the cases of generalized inclusion disease in children which have been described in the literature and including the four cases reported here (Table 2), there have been four stillbirths and 23 live births; 20 of the infants died within three months of birth. Eleven (almost 50%) of the babies born alive died under the age of 28 days. No difference in sex distribution was found. In 22 cases where the sex was mentioned, 11 of each sex were included.

OBSTETRICAL HISTORY. Details of pregnancy were lacking in all but three cases, where it was said to be normal. Delivery was by breech in two cases, forceps were used in one case, while birth was normal in ten cases. Of 16 cases where the length of pregnancy was reported, seven were full term

TABLE 1

SUMMARY OF SIX CASES WITH MINIMAL LESIONS

Case	Age	Sex	Clinical Diagnosis	Necropsy Findings	Sites of Inclusion Cells	Findings not Referable to Primary Disease
5	6 wks.	F	Atresia of oesophagus	Atresia of oesophagus Mediastinal abscess	Lung Liver	Haemosiderosis of liver
6	3 mths.	M	Pneumonia	Cystic fibrosis of pancreas Bronchiectasis Purulent bronchopneumonia	Lungs Kidneys	None
7	3½ mths.	F	Intestinal obstruction	Lobular pneumonia Duodenal ulceration	Duodenum	Inclusion cells associated with duodenal erosions
8	5½ mths.	M	Congenital hydrocephalus	Chronic pyocephalus Internal hydrocephalus	Kidney Salivary gland	None
9	7 mths.	M	Enteritis	Pneumonia. Meningitis Enteritis	Salivary gland	None
10	11 yrs.	F	Chronic glomerulonephritis	Chronic glomerulonephritis	Duodenum Pancreas	None

TABLE 2

SUMMARY OF CASES OF GENERALIZED DISEASES IN LIVE BIRTHS

Author	Age Sex	Foetal Age	Jaundice	Purpura	Enlargement of		Clinical Findings	Blood Changes	Diagnosis	Sites of Inclusion Cells
					Liver	Spleen				
Goodpasture and Talbot (1921)	8 weeks M	Full term			+		Green stools at birth; anorexia; oedema of feet; pus in urine; terminal cough		Cystic fibrosis of pancreas; broncho-pneumonia	Lung, liver, kidney.
Walz (1926)	20 minutes M	Prem.			+	+	Cyanosis; oedema of scrotum and back; ascites		Asphyxia; enlarged thymus	Liver, kidney, pancreas, thyroid
Wagner (1930)	15 days M	34 weeks		+		+	Frequent stools; melaena; haematuria; bleeding from gums and umbilicus. Mother's W.R. positive		Congenital syphilis; pyelonephritis; lung abscess	Lung, salivary gland, liver, pancreas, kidney, thyroid, epididymis
Farber and Wolbach (1932)	20 days F								Haemorrhagic diathesis	Lung, kidney, liver, thyroid, pancreas
	2 days M								Erythroblastosis	Lung, liver, pancreas, kidney
Wanstrom (1933)	6 hours F		+ at birth		+	+	Several cyanotic attacks; ascites	Raised icteric index and serum bilirubin	Erythroblastosis; intracranial haemorrhage	Liver, kidney
McCordock and Smith (1934)	3 months						Cough for several weeks		Cystic fibrosis of pancreas; chronic pneumonia; focal necrosis of liver and adrenals	Lung, adrenal, liver, kidney
Andrews and Miller (1935)	Few hours F	Full term	+ at birth	+				R.B.C.s 3·65 m. W.B.C.s 12,400 Nucleated R.B.C.s 34% Icteric index 43 Prolonged bleeding and clotting times	Erythroblastosis	Lung, kidney, skin
Vidari (1940)	24 hours M	Prem.	+ at birth	+	+	+		Erythroblastaemia; Nucleated R.B.C.s 10%; thrombocytopenia; prolonged bleeding time	Haemorrhagic diathesis	Lung, kidney, liver, thyroid
Kinney (1942)	14 days F	Full term	+ at 12 days				Frequent stools with occult blood at 11 days; anorexia; vomiting; dehydration		Cerebral softening; kernicterus	Lung, kidney, liver, brain, pancreas
Cappell and MacFarlane (1947)	24 hours M	Prem.	+ at birth	+	+			Erythroblastaemia Hb. 110%; nucleated R.B.C.s 54%; serum bilirubin 14 mg. %	Erythroblastosis	Lung, pancreas, liver, kidney

TABLE 2—*continued*

Author	Age Sex	Foetal Age	Jaundice	Purpura	Enlargement of		Clinical Findings	Blood Changes	Diagnosis	Sites of Inclusion Cells
					Liver	Spleen				
Cappell and MacFarlane (1947)	16 hours M	38 weeks	+ at birth	+				No Rh incompatibility	Erythroblastosis	Lung, liver, kidney
Kalfayan (1947)	2½ months M				+	+	Conjunctivitis ; corneal opacities ; enlarged salivary glands; tracheobronchitis	Polymorphonuclear leucocytosis	Bronchopneumonia ; conjunctivitis	Lung, kidney, liver, spleen, pancreas, thyroid, adrenal, eye, salivary gland
Worth and Howard (1950)	6 weeks M	Full term	+ at 3 weeks	+	+	+	Diarrhoea at 3 weeks	No Rh incompatibility	Intracranial haemorrhage	Heart, testis, lung, stomach, spleen, liver, intestine, lymph node, pancreas, brain, adrenal, skin, pituitary, kidney, thyroid
Wyatt, Saxton, Lee, and Pinkerton (1950)	14 months F						Cough and respiratory difficulty for 8 days ; cyanosis ; vomiting ; maculo-papular rash		Pneumonitis	Lung, kidney
	14 months F						Whooping cough for 3 weeks; dehydration		Whooping cough ; pneumonitis	Lung, liver
	13 weeks M			+	+	+	Frequent bloody stools; haematemesis	R.B.C.s 2·4 m. Platelets 80,000 ; No Rh incompatibility	Congenital thrombocytopenia ; bronchopneumonia	Lung, kidney, liver, ileum, pancreas, brain, adrenal
	7 weeks M		+ at 6 weeks		+	+	Upper respiratory infection; diarrhoea; melaena; haematemesis; haematuria; oliguria; generalized oedema	R.B.C.s 3·2 m. ; Icteric index 150; Prothrombin index 75% of normal	Hepatitis with fibrosis; pneumonitis	Lung, pancreas, liver, brain
	5 weeks F		+ at birth	+	+	+	Diarrhoea; cephalin-cholesterol test strongly positive	Erythroblastaemia ; platelets depressed ; prolonged bleeding time; no Rh incompatibility	Erythroblastosis ; Obstructive biliary cirrhosis; pneumonitis	Lung, kidney, liver, thyroid, pancreas, parathyroid, salivary gland
Present Author	4 months F	Full term	+ at birth		+		Constipation followed by diarrhoea; signs of cretinism	Van den Bergh direct positive; serum cholesterol 212 mg. %	Cretinism ; gastroenteritis	Lung, kidney, liver, pituitary, pancreas, thyroid, salivary gland
	14 days F	Prem.	+ at birth	+	+	+	Microcephaly with cerebral calcification ; albuminuria with casts	Hb. 10·9 g. % ; R.B.C.s 2·9 m. ; platelets 10,000	Cerebral calcification; cirrhosis of liver ; cystic fibrosis of pancreas	Lung, kidney, liver, thyroid, pancreas
	3 months F	Prem.					Osteomyelitis of femur; snuffles; stridor; dactylitis; W.R. positive		Congenital syphilis ; osteomyelitis	Lung, kidney, liver, pancreas, parathyroid
	2 months F	7 months	+ at 7 weeks		+		Constipation at birth ; skin rash ; pyuria	Van den Bergh biphasic positive	Pyelonephritis ; pneumonitis	Lung, kidney, liver

babies, while nine varied from 32 to 38 weeks of gestation.

EVIDENCE OF SYPHILIS. Two stillbirths (Jesionek and Kiolemenoglou, 1904; Pisano, 1910) were considered to have congenital syphilis on clinical and pathological grounds only. However, as Cappell and McFarlane (1947) pointed out, the cellular infiltration of the organs in these cases may have been partly due to extramedullary haemopoiesis, so that they possibly fall into the group of cases with evidence of haemolytic disease.

In Case 3 the Wassermann reaction was positive, while in Wagner's case (1930), the mother's serum was positive and the child's negative. In 13 other cases either the mother or child had negative reactions. It appears unlikely that the presence of syphilis was anything but coincidental, although it may have predisposed the infants to infection by the salivary gland virus.

STILLBIRTHS. Except for the presence of inclusion cells in the kidneys, liver, and lungs, the case reported by Smith and Weidman (1910) showed no disease. These cells were present in appreciable numbers only in the kidneys where they were associated with an inflammatory reaction. In their series Wyatt, Saxton, Lee, and Pinkerton (1950) include a single stillbirth in which they demonstrated mild interstitial pneumonitis associated with inclusion cells. Two cases with inconclusive evidence of syphilis have already been mentioned. In none of these cases was purpura, jaundice, or hepatosplenomegaly noted. Walz (1926) described a premature boy who lived for 20 minutes, and in whom ascites was the most prominent feature.

HAEMOLYTIC DISEASE. That generalized infection by the salivary gland virus is often associated with haemolysis or a bleeding tendency is shown by the fact that of 23 live births reported in the literature no less than six clinically resembled erythroblastosis and two were diagnosed as 'haemorrhagic diathesis.' Six of these eight cases died within two days of birth. One case lived for 20 days (Farber and Wolbach, 1932), while another, which presented similar signs shortly after birth, survived for five weeks, finally dying with clinical and pathological evidence of cirrhosis (Wyatt *et al.*, 1950, Case 6). In only three cases was the possibility of Rh incompatibility eliminated (Cappell and McFarlane, 1947; Wyatt *et al.*, 1950).

Excluding the two cases mentioned by Farber and Wolbach (1932), where no details were given, and which were diagnosed as erythroblastosis and haemorrhagic diathesis respectively, the clinical features of the remaining cases were remarkably similar. Jaundice was present at or within a few hours of birth in all cases, and petechiae of the skin were present in five. Hepatosplenomegaly, often of marked degree, was usually present. Ascites was demonstrated clinically only once (Wanstrom, 1933), although slight ascites was occasionally found at necropsy. The red cell count was sometimes slightly below normal, the lowest recorded being 3·65 million per c.mm. (Andrews and Miller, 1935) whilst the haemoglobin level was usually within normal limits. The white cell count was usually normal with nucleated red cells representing 10 to 54% of the total nucleated elements. The bleeding time was stated to be prolonged in three cases, in one of which (Andrews and Miller, 1935) the clotting time was also prolonged. Thrombocytopenia was observed by Vidari (1940), and by Wyatt *et al.* (1950), in whose case a level of 23,000 per c.mm. was reached. The icteric index was raised in two cases, and in a third the serum bilirubin level was 14 mg. %. Except for the presence of inclusion cells in a number of organs, the pathological findings were similar to those of erythroblastosis foetalis. Extramedullary haemopoiesis was always present in the liver and spleen, and was often found in the kidneys, lungs, pancreas, and other organs. Haemosiderin deposits tended to be small and, when present, were mainly in the liver.

It is noteworthy that in three other cases the question of erythroblastosis was raised. Case 2 in the present series showed jaundice and skin petechiae with marked hepatosplenomegaly, thrombocytopenia, and a blood count with three nucleated red cells per 100 white cells. The pathological findings could be explained on the basis of its being a case of erythroblastosis, although it was felt that the cerebral calcification was due to infection by toxoplasma. A minor degree of cerebral calcification was noted by Wanstrom (1933), who described calcified thrombi in the brain, and by Wyatt *et al.* (1950, Cases 4 and 6) who believed that it represented ependymitis. The high incidence of cerebral calcification in this group leads one to consider the possibility that it is due in some way to the viral infection, although conclusive evidence of such infection in the lesions is usually lacking.

Case 4 of Wyatt *et al.* (1950) also showed evidence pointing towards an initial diagnosis of erythroblastosis, but here thrombocytopenia and diffuse purpura dominated the picture. Thrombocytopenia has been observed on four occasions in the neonatal period, and appears to be a significant feature of the blood picture in those infants with signs of haemolytic disease.

Kernicterus has been reported only once (Kinney, 1942). This 14-day-old child developed jaundice three days before her death, but showed no obvious clinical or pathological signs of erythroblastosis.

Irregular yellow areas of cerebral softening were found, associated with one of which was a single inclusion cell.

It may be concluded that where infection is present at birth a large percentage of cases clinically resemble erythroblastosis foetalis, purpura and thrombocytopenia often being prominent features. Infection by the salivary gland virus should be considered in the differential diagnosis of any newborn child with icterus, hepatosplenomegaly, and the blood picture of erythroblastosis foetalis in whom no blood group incompatibility can be demonstrated.

PULMONARY INVOLVEMENT. The clinical picture was dominated by evidence of pulmonary pathology in only two cases (Wyatt *et al.*, 1950, Cases 2 and 3). Both were 14 months old, and had suffered from pertussis for three weeks before death. The symptoms, signs, and x-ray findings were equivocal but at the necropsy the lungs showed septal pneumonitis with a lymphocytic and mononuclear inflammatory reaction associated with numbers of inclusion cells. Neither case presented any history suggestive of haemolytic disease. Kalfayan (1947) reported the case of a child of 2½ months who died of bronchopneumonia following intractable suppurative conjunctivitis. No signs or symptoms referable to the lungs were found other than those of bronchopneumonia. Histological examination of the lungs showed areas of fibrosis and round cell infiltration together with numbers of inclusion cells. A similar septal pneumonitis was also found in the necropsy of a 13-week-old child dying with purpura and thrombocytopenia (Wyatt *et al.*, 1950, Case 4).

The existence of pneumonitis in cases of generalized viral disease is of interest when the observations of workers on the lungs of children dying of pertussis are considered. Feyrter (1927) was the first to observe inclusion cells identical with those produced by the salivary gland virus in the alveoli and peribronchial tissues of a 2½-year-old girl dying of pertussis and measles. In 1932, Rich found similar cells in five cases of whooping cough, but he emphasized that, as only two showed any appreciable infiltration of the bronchial walls, one should guard against considering such a reaction as being caused by a virus. McCordock and Smith (1934) demonstrated typical inclusion cells in the lungs of 18 out of 40 cases of pertussis dying between the ages of a few weeks and 5 years. They also found inclusion cells in the lungs of five children between 3 months and 2 years who at necropsy showed chronic pneumonia with peribronchial infiltration. Kinney (1942) added four similar cases of clinical whooping cough. While it is possible that this is merely an incidental association, some other explanation is more likely. The condition clinically resembling whooping cough may be a distinct entity caused by the virus; a latent endogenous virus may be activated by infection with the *Haemophilus*, or the virus may enter the lungs as a secondary invader (McCordock and Smith, 1934).

Of equal interest is the finding of inclusion cells in the lungs of children with cystic fibrosis of the pancreas. This was first described by Goodpasture and Talbot (1921) who found large numbers of inclusion cells in the inflammatory areas of the lungs, especially within the walls of the chronically inflamed bronchi. Two other cases were mentioned by McCordock and Smith (1934). In none of these were inclusion cells present in the pancreas. They have, however, been described on 13 occasions in the acini and ducts of the pancreas in the absence of cystic fibrosis. No conclusions can be based on such a small series, especially when one considers that the presence of these cells in a single organ, particularly the salivary glands, is not uncommon.

HEPATITIS. Clinical and pathological evidence of hepatitis or cirrhosis has been noted in three cases. A 7-week-old boy described by Wyatt *et al.* (1950, Case 5) after an initial history of acute otitis media, vomiting, and diarrhoea, showed progressive hepatosplenomegaly, and during the last week of life, severe jaundice. Bile was constantly present in the urine. Hepatitis was diagnosed during life, and at necropsy centrilobular necrosis and periportal fibrosis were found in the liver. Case 6 of these authors, a 5-week-old girl, resembled erythroblastosis foetalis during the neonatal period, but during the last two weeks of life showed evidence of liver damage. Urobilinogen and bilirubin were present in the urine, and the cephalin-cholesterol flocculation test was strongly positive. Necropsy showed obstructive biliary cirrhosis with degeneration of the liver cells in both central and peripheral zones of the lobules. Although there was no clinical suggestion of liver disease in Case 2 in the present series, biliary cirrhosis was found at necropsy.

In view of the frequency with which obstruction of the small biliary ducts occur, it is not surprising that, when life is prolonged beyond the neonatal period, some form of liver damage should supervene. Mild cirrhosis could be the direct result of the obstruction to the flow of bile, although it is difficult to explain the production of the histological lesions of typical virus hepatitis on these grounds. There is little evidence to suggest that the salivary gland virus exerts a necrotizing effect. On the contrary, the lesions in this disease are usually free of necrosis.

PYELONEPHRITIS. The kidneys are almost invariably affected in the generalized disease, often showing the most marked pathological lesions. Although the inclusion cells are usually surrounded by a mild inflammatory reaction, acute inflammation has only been seen on two occasions. Wagner (1930) found haemorrhagic cystitis and ascending pyelonephritis with abscess formation in a 15-day-old syphilitic child, a condition which was not suspected during life. Case 4 in the present series showed numerous pus cells in the urine and ascending pyelonephritis was demonstrated at necropsy. These cases are undoubtedly due to superadded infection rather than to the action of the salivary gland virus. It is rare to find any changes in the urine referable to kidney disease even when the kidneys are extensively involved, although Wyatt *et al.* (1950) have suggested that inclusion cells may possibly be found in the urine during life.

ENDOCRINE INVOLVEMENT. Involvement of the endocrine glands is comparatively frequent. Inclusion cells were present in the adrenal glands in five cases, in the parathyroids in two cases, and in the pituitary gland in one case. They have been found in the thyroid gland in no less than nine cases of generalized disease (Walz, 1926; Wagner, 1930; Farber and Wolbach, 1932; Vidari, 1940; Kalfayan, 1947; Worth and Howard, 1950; Wyatt *et al.*, 1950; Cases 1 and 2 of the present series), and as an isolated finding in one case (Pettavel, 1911). Only in Pettavel's case was endocrine dysfunction noted, the lesions in the thyroid being associated with neonatal goitre.

The presence of definite thyroiditis in Case 1 with numerous foci of inflammation diffusely scattered throughout the gland, and the fact that lesions were more numerous in the thyroid than in any other organ, suggest that the infection may have caused signs of hypothyroidism by its direct action on the thyroid gland. The gland, however, was abnormal in other ways. The acini were small, the lining cells were irregular and appeared to have proliferated, and there was a total absence of any evidence of active secretion. The picture was quite unlike that usually seen in cases of cretinism. It is difficult to visualize how a focal inflammation could have caused such generalized histological changes, especially when one considers that most of the cases previously described showed no such changes. The pituitary gland was directly involved and this may have secondarily inhibited thyroid activity. Although no definite conclusions can be drawn as to the actual mechanism involved, it appears certain that a connexion exists between the infection, its localization in the thyroid and pituitary glands, and the presence of hypothyroidism.

GASTRO-INTESTINAL SYMPTOMS. Whilst the incidence of diarrhoea was high (eight of 23 cases), it was usually impossible to relate this to infection by the virus. The onset of the diarrhoea varied within wide limits, sometimes occurring within a few days of birth, at other times not appearing until shortly before death. Its severity was likewise very variable. In four cases diarrhoea was associated with vomiting.

Hepatomegaly, usually with splenic enlargement, was recorded in 13 cases. In the majority of these it was quite independent of any gastro-intestinal symptoms, although, as in Case 1, the degree of enlargement sometimes varied with the severity of the diarrhoea.

Inclusion Cells in Single Organs Only. Typical lesions have been observed in single organs of children dying of a great variety of diseases. Only in the case of neonatal goitre (Pettavel, 1911), and in those cases of whooping cough (McCordock and Smith, 1934, and others), did their presence in the body appear to have been significant.

Where routine examinations of the salivary glands have been performed inclusion bodies were found in a high percentage of children. The series of Farber and Wolbach (1932) where inclusion cells were found in the salivary glands of 24 of 183 consecutive necropsies, confirmed observations on their occurrence by Ribbert (1904), Lowenstein (1907), and Wagner (1930). Further cases by McCordock and Smith (1934) and Kinney (1942) have produced 42 cases with lesions in the salivary glands only. In eight cases they were found in the kidneys only, usually in the convoluted tubules, and almost invariably associated with a mild inflammatory reaction. It is noteworthy that one of these had cirrhosis (de Lange, 1922) and another hepatitis (Müller, 1922), although those described by Ribbert (1904), Lowenstein (1907), Jackson (1922), and Silbergleit (1938) showed unrelated lesions.

Mouchet (1911) found typical cells in the liver of a case of cirrhosis aged 8 days. The only other incidental finding in the liver was by McCordock and Smith (1934) in a child dying of cerebral haemorrhage.

Summary

Four cases of generalized infection by the salivary gland virus, and six cases with inclusion bodies in one or two organs only are described.

A review of the literature shows early death and frequent prematurity to be common. The most common clinical picture in infants dying within two days of birth is composed of jaundice, purpura, hepatosplenomegaly and erythroblastaemia with diminution of blood platelets. Other common clinical features

are cerebral calcification, cough often associated with pneumonitis, whooping cough, and cystic fibrosis of the pancreas, and gastro-intestinal symptoms, especially diarrhoea.

At necropsy the organs most commonly affected are the lungs, kidneys, liver, pancreas, and salivary glands. Those less commonly affected are the thyroid, adrenals, pituitary, parathyroids, brain, intestine, epididymis, spleen, eye, amd skin. Signs of dysfunction of the affected organs are usually lacking. This is especially true of the endocrine glands, although an exception is found in one case of the present series where thyroiditis with hypothyroidism was present.

While generalized infection must be considered to be a rare condition, affection of one or two organs, particularly the salivary glands, is not infrequent.

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THE DIAGNOSIS OF VIRUS PNEUMONIA IN INFANTS AND CHILDREN

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'The diagnosis of primary atypical pneumonia at the present time is in reality a process of excluding the known specific diseases which may present the same clinical syndrome.' This comment of Dingle's made in 1947 is presumably still true. In infants and children suffering from pneumonia sputum is rarely obtainable, and as Rabe (1948) stated 'the mere presence of a potential pathogen in the rhino-pharyngeal cultures of patients with a respiratory infection does not necessarily mean that the organism is the cause of the disease'. Any attempt at aetiological diagnosis in this age group thus depends on the evaluation of clinical data and the application of such tests as have been reported to be of value in the diagnosis of virus pneumonia. The present report is concerned with an attempt to discover the variations of certain clinical findings in cases of lobar pneumonia in children and with an investigation of two techniques which have been claimed to be of diagnostic value.

Atypical Features in Lobar Pneumonia

So-called primary atypical pneumonia differs clinically from primary bacterial pneumonias in four respects: gradual onset (Reimann, 1947), discrepancy between clinical and radiographic findings, absence of leucocytosis, and failure to respond rapidly to sulphonamides or penicillin.

Israel, Mitterling, and Flippin (1948) refer to the characteristic marked leucocytosis and the dramatic response to sulphonamides or penicillin as 'the two criteria that formerly seemed most valuable in the differentiation of bacterial and viroid pneumonias'. In order to assess the validity of these criteria it is necessary to know the range of these findings in typical cases of pneumonia. The data presented here concern cases of lobar pneumonia in infants and children.

Material. All the cases of lobar pneumonia admitted to the medical wards of the Royal Edinburgh Hospital for Sick Children from April, 1947, to March, 1949, inclusive have been studied. The information required has been extracted from the case reports; 267 cases are included. In these the diagnosis was established at necropsy in four instances, by radiography in 247, and by clear-cut and characteristic clinical signs in 16. All cases of pneumonia—bronchopneumonia, terminal pneumonia, and other atypical forms of pulmonary infiltration—except those which seemed on the basis of the available information to be true lobar pneumonia have been excluded from the study. The age distribution of the cases was very similar to that reported previously from this hospital (McNeil, Macgregor and Alexander, 1929; McNeil, 1939).

Results. The results are discussed under the headings type of onset, comparison of clinical and radiological findings, leucocyte response, and response to chemotherapy.

TYPE OF ONSET. In four instances the recorded information is not sufficiently detailed to justify their inclusion. Of the remaining 263 cases two main subdivisions could be established; 175 of these patients were cases of acute onset who had been ill for an average period of only three days before admission. In the other 88 cases the duration of the illness before admission to hospital was considerably longer; the average was 18 days. These two groups will be considered separately.

Cases of Short Duration. In 124 instances the child was said to have been quite well before the onset of the acute symptoms. In the remaining 51 cases there was a short period of ill-health before the onset of the fever. Twenty-seven of these were reported to have had an acute upper respiratory infection for a few days; in the other 24 the

prodromal illness was characterized by malaise and anorexia without any localizing symptoms. The onset of pneumonia was generally heralded by the appearance of fever, cough, and some respiratory upset. Rigors were uncommon, being reported in only six cases. Rather unexpectedly convulsions were even rarer; they were recorded in only three infants under the age of 2 years.

Cases of Long Duration. These fall into four groups. (1) In 26 cases an acute respiratory illness (variously labelled pneumonia, congestion of the lungs, influenza, etc.) was treated at home with a sulphonamide preparation and admission to hospital sought because of unsatisfactory response or relapse on the discontinuance of treatment. (2) In 27 cases the illness was of low grade and some persistence. The characteristic story was of irregular fever with cough and general malaise lasting for a period of a week or longer, without any marked deterioration and without any apparent tendency to improvement. (3) A further 22 cases had progressive illnesses starting usually with a cold and developing cough, fever, disturbed breathing, chest pain, and other symptoms in deliberate succession but without any clear-cut acute episodes. (4) The final group of 13 cases included a variety of symptom complexes. In most of them respiratory symptoms were not prominent and the illnesses were not suspected to be pneumonia until after admission to hospital. They include children referred with joint pains, persistent vomiting, diarrhoea, and abdominal pain.

If the cases treated at home are excluded (on the grounds that the information about the original onset was usually rather inexact) there are left 237 cases for which detailed histories of the onset are available. Of these 175 (74%) had an acute onset and 62 a subacute onset. This is in accordance with previous reports. McDermott (1946) states that in about three-quarters of cases of lobar pneumonia the onset is sudden. In Heffron's (1939) series of 949 cases the onset was sudden in 70%.

Thus in these 237 cases the disease began abruptly and without warning in 124 (53%). Forty-nine (21%) started with symptoms of an acute upper respiratory infection, and in these the onset of the pneumonia was sudden in 27 and insidious in 22. In 51 (21%) a period of indefinite malaise preceded the pneumonia, and of these 24 had an acute onset of symptoms of pneumonia, while in 27 the onset was insidious. In the remaining 13 cases (6%) the onset was bizarre and unusual.

Comparison of Clinical and Radiological Findings. Table 1 summarizes the information obtained from a comparison of the recorded clinical signs and scrutiny of the radiographs. The term 'signs of consolidation' indicates that at some period of the child's stay in hospital signs were detected in the chest which could be interpreted as evidence of pulmonary infiltration. In many cases these signs were by themselves inconclusive, for example, merely diminution of air-entry at one area, but where they were confirmed by radiography they have been accepted as clinical evidence of consolidation.

It is clear from these figures that a discrepancy between physical signs and x-ray findings in children cannot be used as a diagnostic criterion as between lobar and atypical pneumonia.

Leucocyte Response. Table 2 shows the distribution of the leucocyte counts in the cases of acute and subacute onset. Only counts performed within the first three days of admission have been included in this table. These figures indicate that over 10% of these children had white cell counts of less than 10,000 cells per c.mm.

Response to Chemotherapy. In the two years covered by this survey the only powerful drugs generally available for the treatment of pneumonia were sulphonamide preparations and penicillin. These were given to 165 of the cases of acute onset and to 58 of those with subacute onset (85% of the total number). The response of these cases has been judged by the rate of decline of fever after the start of therapy. In each case a note was made of the

Table 1
Summary of Radiological Evidence

Age Group (years)	Total	No. of Radio-graphs	Radiologically Positive with Clinical Signs of Consolidation	Radiologically Negative with Clinical Signs of Consolidation	Radiologically Positive with No Clinical Signs of Consolidation
0–2	87	84	53	7	24
2–5	80	80	65	4	11
5–12	100	99	90	5	4
Total	267	263	208	16	39 (15%)

TABLE 2

DISTRIBUTION OF LEUCOCYTE COUNTS IN CASES OF ACUTE AND SUBACUTE ONSET

	No. of Counts	Below 10,000	10,000–15,000	15,000–20,000	Over 20,000
Acute onset ..	164	12	39	44	69
Subacute onset ..	84	17	17	20	30
Total	248	29 (11·7%)	56 (22·6%)	64 (25·8%)	99 (40%)

day on which the temperature returned permanently to normal following the inception of chemotherapy. The results are shown in Table 3. It will be noticed that, while over three-quarters of the patients became afebrile within 48 hours of the start of specific therapy, in about 15% the response was appreciably slower. In fact two distinct types of response could be observed. One was a dramatic fall of temperature generally within 48 hours of starting treatment; the other was a more gradual fall by lysis which in some cases took as long as a week before the temperature became permanently normal. This difference has been commented on before. McDermott (1946) notes that in 85% of his cases treated with penicillin the fever subsided by crisis and in the rest more gradually. Kinsman, Daniels, Cohen, McCracken, D'Alonzo, Martin, and Kirby (1945) reported that of cases treated with sulphadiazine about 10% responded considerably more slowly than the average. These figures are in substantial agreement with those observed in the present series.

It is apparent then that 10 to 15% of cases of lobar pneumonia treated with sulphonamides or penicillin exhibit a retarded response to these drugs and that caution is required in any individual case in deciding that this delay indicates that the pneumonia is in any other way ' atypical.'

Summary. In 267 cases of apparently true lobar pneumonia in infants and children the range of variation of four features has been determined. These were the type of onset, the leucocyte response, correlation of clinical and radiographic findings, and the response to chemotherapy. In each of these respects a small but not negligible number of cases showed unusual features and it is contended that the term ' atypical ' as applied to the pneumonias of childhood is merely descriptive and cannot be given any aetiological significance.

Cold Agglutinins and Virus Particles in Children

This section concerns an investigation on an unselected group of infants and children suffering from acute respiratory disorders which was undertaken in an attempt to evaluate two techniques which have been claimed to be of diagnostic value in these conditions.

Material. The cases investigated were those infants and children admitted to the Children's Hospital and the City Hospital, Derby, during a three-month period in 1950, who were suffering from acute bronchitis and pneumonia. It was not possible to examine every such admission for a number of reasons (such as rapid death, early discharge from hospital, and occasionally because of technical difficulties), but the cases were quite unselected and were a representative group of acute bronchopulmonary infections in patients ranging from 3 weeks to 13 years of age. A number of children suffering from other disorders in the

TABLE 3

ANALYSIS OF EFFECT OF ANTIBIOTICS ON PYREXIA IN DAYS

Drug Used	Total Treated	Afebrile Throughout	*T.N. in 24 Hours	T.N. by End of 2nd Day	T.N. by End of 3rd Day	Febrile over 3 Days
Sulphonamide ..	124	15	42	93	102	7
Penicillin ..	41	6	19	29	30	5
Sulphonamide + penicillin ..	58	5	13	20	36	17
Total ..	223	26	74 (37·6%)	152 (77·2%)	168 (85·3%)	29 (14·7%)

* T.N. = permanent abatement of fever.

same wards at the same time were similarly examined.

Methods. Besides the usual clinical and pathological examinations cold agglutinin tests were performed on the serum, and pharyngeal swabs were examined for intracellular inclusion bodies. The cold agglutinin tests were performed whenever possible in the second week of the illness (the average period from the onset of the respiratory disease to the performance of the test was 11½ days) and thereafter as indicated. The technique used was that of Young (1946). Pharyngeal smears were made as early in the course of the disease as possible and were occasionally repeated. The stain employed was Mann's stain (G. T. Gurr). With this stain the particles are easily detected, showing up as bright red, refractile, regular bodies within the cytoplasm of the epithelial cells, generally close to the cell nucleus. Fig. 1 shows a typical body from one of the children in this series.

FIG. 1.—Typical particle after Mann's stain.

Results. The results are discussed first as regards the test, and secondly as relating to the inclusion bodies.

COLD AGGLUTININ TESTS. One hundred and sixty-nine tests were performed on 114 patients, of whom 66 were suffering from acute pneumonia or bronchitis and 48 from a variety of other conditions. Fig. 2 shows the maximum titres obtained in the various groups. Of the 49 cases of pneumonia, 34 were typical acute lobar pneumonia, 13 were diagnosed as primary bronchopneumonia, and the remaining two were cases of lobar pneumonia with delayed resolution. The ' miscellaneous respiratory disease ' group included cases of upper respiratory infection (tonsillitis, pharyngitis, otitis media), pulmonary tuberculosis, post-operative pulmonary collapse, fibrocystic disease of the pancreas, bronchiectasis, etc. The ' other conditions' group comprised cases of infective hepatitis, glandular fever, chorea, rheumatic heart disease, epilepsy, chronic skin sepsis, etc.

Young (1946) regards a single titre of 1:128 as being of significance in the diagnosis of virus pneumonia, or a titre of 1:32 if there is evidence of the appearance of the agglutinins with the infection or their disappearance after it. Using this criterion significant titres were encountered in 26 cases in all. Table 4 shows the number of such titres in the various groups.

In the pneumonia group 12 of the patients with significant titres were suffering from acute lobar pneumonia, one from lobar pneumonia with delayed

resolution, and four from bronchopneumonia. None of these was regarded, clinically, as being a case of virus pneumonia.

Of the children in the ' miscellaneous respiratory ' group showing high or rising titres, one was a case of fibrocystic disease of the pancreas with the chronic staphylococcal bronchopneumonia commonly encountered in that disease, two were suffering from

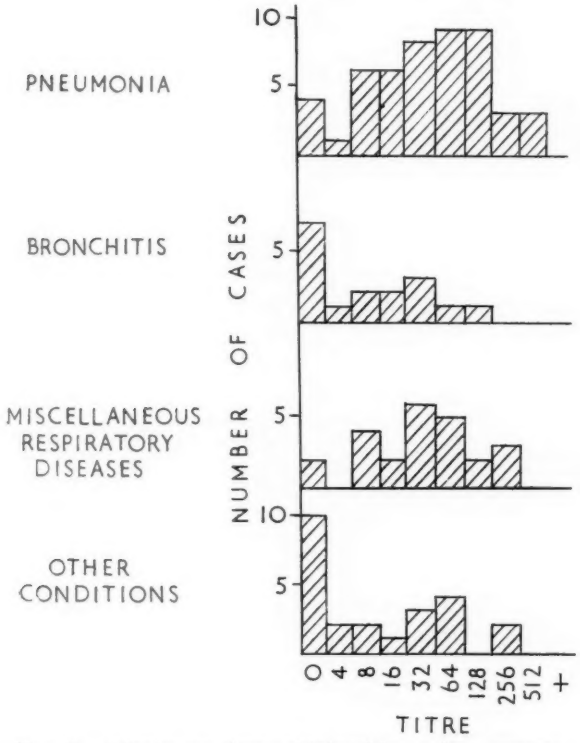

FIG. 2.—Maximum titres obtained in various groups.

primary tuberculous infection of the lungs, one had massive collapse of the left lower lobe following laparotomy, one was a case of hepatic cirrhosis in whom an unsuspected pulmonary infiltration was discovered on radiography of the chest, and the final case was a child who was admitted with acute otitis media two weeks after an acute cararrhal infection of the lungs. The significant titres in the final group were encountered in a child with Banti's syndrome and in a child with multiple superficial injuries after a road accident. In neither of these was there any evidence of pulmonary damage.

Altogether there were 60 children who were proved to have some involvement of the lung parenchyma—acute pneumonia, unresolved pneumonia, pulmonary tuberculosis, post-operative collapse, radiographic opacities not suspected clinically—and 54 in whom there was no evidence of such a lesion. In the former group 22 cases, or 36·7%, had cold agglutinin titres which were significant according to Young's criteria, whereas

TABLE 4

ANALYSIS OF SIGNIFICANT TITRES IN VARIOUS GROUPS

Disease	Total	Significant Titres
Pneumonia	48	17 (34·7%)
Bronchitis	17	1 (6%)
Miscellaneous respiratory diseases	24	6 (25%)
Other conditions	24	2 (8·5%)
Total	114	26 (23·7%)

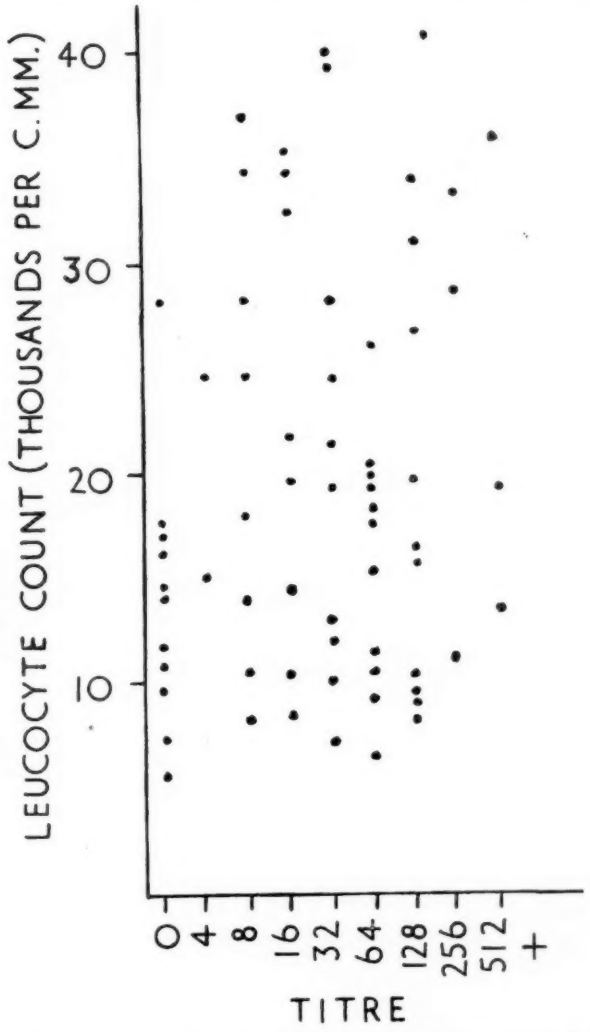

FIG. 3.—Correlation of titres of cold agglutinins with leucocyte response.

in the latter group only four produced such titres, an incidence of 7·4%.

An attempt was made to correlate the titres of cold agglutinins with the leucocyte response in the cases of acute respiratory infection. Fig. 3 shows the result of this investigation. The highest titre attained in each case is shown. There is no apparent relation between the two findings, the leucocyte counts ranging over a wide area at each level of titre.

These children were treated with a number of chemotherapeutic agents—sulphonamides, penicillin, streptomycin, aureomycin, and chloramphenicol—singly and in a variety of combinations. Because of this multiplicity of forms of treatment and the small numbers involved, no precise estimate of the response to chemotherapy of the cases with high and low titres could be formed. However, an attempt was made to detect differences in their behaviour by taking as the index of response permanent abatement of fever within three days of the start of treatment. The cases receiving chloramphenicol or aureomycin have been omitted because of the reported actions of these substances on virus pneumonias. The results in the remaining cases of acute bronchopulmonary infection, i.e. those treated with sulphonamide, penicillin and/or streptomycin, are given in Table 5. The difference in the two groups is not significant.

INCLUSION BODIES. The frequency with which these bodies were recovered in the whole series is shown in Table 6.

As with cold agglutinins an attempt was made to correlate the presence of pharyngeal inclusions with leucocyte counts and the response to chemotherapy. Since the numbers of positive and negative cases are so unequal no definite conclusions could be drawn, but there was no indication of any direct relationship. The average white cell count in the positive cases was 20,700 cells per c.mm., and in the negative cases 18,800 per c.mm. In both groups approximately 65% of the children became afebrile within 72 hours of the start of treatment.

The status of the cold agglutinin test is obscure. Young (1946) examined 1,762 sera from patients with a large variety of diseases and concluded that the test was of definite value in the diagnosis of primary atypical pneumonia. He found significant titres, apart from that disease, only in rubella, infectious mononucleosis, and certain disorders associated with splenomegaly. On the other hand Savonen (1950), basing his conclusions on the examination of 6,971 specimens (the test was performed on every specimen of serum sent for Wassermann examination), stated that 'cold agglutination primarily is brought about by an injury to the lung,' and he could detect no relation between the clinical type of the lung lesion and the titres attained. The present small series, which differs from Savonen's in that the tests were performed at the optimum period and were repeated when indicated, seems to support this conclusion. No relation between the titres of cold agglutinins and the type of pulmonary lesion, its extent, its duration, the leucocyte count, or the response to chemotherapy, could be established, and the primary determining cause would appear to have been involvement of the lung substance in a pathological process. When this occurred high or rising titres of cold agglutinins were encountered five times as often as in its absence.

Adams (1948); Adams, Green. Evans, and Beach (1942); Adams, Pennoyer, and Whiting (1946) have expressed the opinion that the discovery of inclusion bodies in the pharyngeal epithelium is of value in the diagnosis of virus pneumonia. Gedgoud (1943) found these bodies in 35 of 52 persons suffering from a number of different diseases and also in healthy persons. He stated that on his findings 'doubt is cast on the significance of cytoplasmic inclusion bodies as an aid to the diagnosis of the syndrome' (virus pneumonia). Broadhurst, MacLean, and Taylor (1943) also found these intracellular structures in the throats of 65% of 224 apparently healthy students. Although in the present series there is a greater incidence in the cases of acute respiratory infection than in the others it is clear that in any individual

TABLE 5

RESULTS OF ACUTE BRONCHOPULMONARY CASES TREATED WITH ANTIBIOTICS

Temperatures Normal	Significant Titres	Others
In 72 hours ..	11 (65%)	26 (70%)
Over 72 hours ..	6 (35%)	11 (30%)

TABLE 6

FREQUENCY OF RECOVERY OF INCLUSION BODIES

Disease	Inclusions Present	No Inclusions	Total
Pneumonia ..	36 (88%)	5	41
Bronchitis ..	13 (72%)	5	18
Miscellaneous respiratory diseases ..	8 (67%)	4	12
Other conditions ..	8 (53%)	7	15
Total ..	65 (76%)	21	86

case the presence of cytoplasmic inclusions in the pharyngeal epithelium cannot be regarded as evidence of an active virus infection.

Summary. Cold agglutinin tests were performed on 66 infants and children with acute broncho-pulmonary infections and on 48 controls during a three-month period in 1950. High or rising titres were encountered five times more often in the presence of pulmonary damage than in its absence, It is suggested that the phenomenon is a non-specific reaction to pulmonary injury.

Swabs of pharyngeal epithelium were stained for cytoplasmic inclusion bodies in 59 patients with acute respiratory infections and in 27 controls. They were found in three-quarters of the patients examined, and in cases of acute chest disease no relationship could be established between their presence and any other clinical or pathological findings.

It is concluded that neither of these techniques yields reliable evidence of the activity of viruses in acute pulmonary infections.

Conclusions

It would appear from the above considerations that the diagnosis of ' virus ' pneumonia in infants and children does not rest on any secure basis. The term should probably be avoided except in cases such as influenza and psittacosis where definite proof of the activity of a known virus can be established. Claims for the effectiveness of chemotherapeutic agents in a condition of such doubtful authenticity should accordingly be treated with reserve.

I am indebted to Professor R. W. B. Ellis, Dr. D. N. Nicholson, and Dr. J. L. Henderson, of the Royal Edinburgh Hospital for Sick Children, for permission to consult the records of their cases; to Dr. D. V. Hubble and Dr. E. J. S. Woolley for allowing me to investigate the cases in their charge in Derby; to Dr. G. R. Osborn for the provision of pathological facilities; to the laboratory staffs of the Derby hospitals for assistance; and to Mr. J. Fayers for the microphotograph. I wish to thank Professor Ellis for advice on the presentation of this material.

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CONGENITAL HEMIATROPHY OF THE BRAIN

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Hemiatrophy of the brain may occur in adults and in old age as a result of degenerative or vascular disorders, but the name is more commonly applied to the congenital or the infantile variety of the condition. It was proposed by Alpers and Dear (1939) that the two varieties be designated secondary and primary respectively. The condition is, however, always secondary in the sense that it is due to some cause which is frequently ascertainable. It is therefore better to speak of the adult and of the congenital (or infantile) varieties of hemiatrophy. The object of this report is to present a case and to discuss some pathological aspects of such congenital hemiatrophy.

The reduction in size of the brain in such cases is caused by loss of nerve tissue and its replacement by glial scars. The replacement is, in some cases, inadequate, and foci of acellular necrosis as well as cysts are frequently found. The larger cysts are usually filled with clear fluid, while the smaller ones may contain debris with fat and blood pigment phagocytes. Concomitant findings may include granular atrophy of gyri, ulegyria, status spongiosus, status marmoratus, thickening of blood vessels, mesenchymal proliferation, meningeal fibrosis, and hydrocephalus.

The extent and severity of the lesions are, by definition, more marked on one side, but the condition is seldom, if ever, strictly unilateral, some degree of scarring being also present in the second hemisphere. The basal ganglia may likewise be reduced in size on the affected side and this is accompanied by a crossed cerebellar atrophy. This association enabled Mott and Tredgold (1900) to deduce that such cerebellar atrophy depends on the involvement of the basal ganglia. Glial scars may also be found in the brain stem.

It was suggested by Schob (1930) that cerebral hemiatrophy comprises two distinct conditions: a variety of lobar scarring or ulegyria in which the lesions extend beyond a single lobe to affect a whole hemisphere and, secondly, progressive sclerosing hemiatrophy. Parenchymal loss is more uniform and usually less severe in the second condition, and the lesions are found chiefly in one of the cortical laminae, especially the third. Areas of focal destruction are uncommon. Blood pigment and fat-laden phagocytes are less numerous and are scattered more diffusely through the cortex, while the gliosis affects chiefly the digital white matter and is restricted in the cortex to its margin and the third lamina. Clinically, the condition is characterized by a more progressive mental deterioration and epilepsy. The existence of this distinct variety of hemiatrophy has been endorsed by Töppich (1935) and by Josephy (1945).

One of the earliest cases of cerebral hemiatrophy was reported by Charcot and Turner (1852). They found it in a mentally defective epileptic woman aged 20, and quoted Cazanviech and Calmiel as originators of the term '*atrophie ou agénesie cérébrale*' which they themselves used to designate this condition. By 1861, when the Dutch anatomist Schroeder van der Kolk contributed a scholarly description of a case, which, in the manner of his time, was both long and detailed, there were already 29 similar cases on record. Later contributions included those of Howden (1875), Major (1879), Mott and Tredgold (1900). Köppen (1905), Spielmeyer (1906), Boyd (1912), Bielschowsky (1917), Stroh (1925), Brushfield and Wyatt (1927), Pekelsky (1932), Hassin (1935), Casamajor and Laidlow (1939), Alpers and Dear (1939), Liber (1940), Moore (1943), and Josephy (1945).

Most of the patients described in the literature have been mental defectives, others were cases of Little's disease, of hemiplegia, with or without extrapyramidal signs, and of epilepsy. Many cases have been diagnosed correctly during life and such diagnosis usually rested on the history, the neurological and psychiatric signs, and the radiological findings. The latter have been the subject of

contributions by Dyke, Davidoff, and Masson (1933), Casamajor and Laidlow (1939), and by Ross (1941).

There is no reason, if one reserves temporarily the consideration of the so-called progressive sclerosing hemiatrophy, to discuss the aetiology of this condition separately from that of the large and varied group of sclerotic and cystic infantile encephalopathies, of which hemiatrophy is merely a topographical variant. The condition may be associated with the presence of true malformations such as microgyria pointing to an intra-uterine onset of at least part of the disorder. It may follow intra-uterine injury as in the case reported by Seitz (1907). Another form of hemiatrophy is associated with a haemangiomatous malformation of the meninges on the brain and may form a part of the Sturge-Weber syndrome. On the other hand, it may develop after birth, as in the case reported by Heubner (1882), where porencephaly was due to an embolus. In the case communicated by Stroh, hemiatrophy was caused by a subdural haematoma occurring as a result of infantile scurvy. Intra-uterine infection as a possible aetiological agent has been discussed by Alpers and Patten (1936). The pathogenetic mechanisms leading to the formation of scars and cysts have also been the object of numerous contributions. Oedema was believed to be the chief mechanism involved by Hallervorden (1939), asphyxia by Courville (1950), anoxia due to a disturbance of the autonomic control of circulation by Rydberg (1932), venous thrombosis by Marburg and Casamajor (1944). A lytic ferment liberated from damaged myelin was suggested as a possible cause of cystic degeneration by Lumsden (1950).

It is necessary at this stage to refer to the opinion of Scholz (1933 and 1936), who thought that certain cerebral lesions might, in some cases, be the result of epilepsy. Such lesions could include diffuse or patchy gliosis, areas of loss of nerve cell and ulegyria, and may account for the ensuing mental deterioration. He did not, however, believe that areas of complete softening followed by the formation of cysts could be caused in this way. The opinion of Scholz has found some cautious support which was expressed by Meyer (1939) as follows:

> 'Though this is certainly not the rule, it may be correct in certain otherwise obscure cases of infantile progressive mental and neurological deterioration with a long initial history of epilepsy and with post-mortem findings of the type described above.'

Ever since the publication of the classical paper by Little (1862) there has always been a current of opinion which regarded the processes of birth as an important factor in the causation of such infantile encephalopathies. A considerable number of morbid anatomical studies of neonatal and infantile brain material was undertaken by Schwartz (1924, 1927), Schwartz and Berberich (1924), Schwartz and Fink (1925), by Ylppö (1919), Siegmund (1923), and by Rydberg (1932). These contributions are of great importance since the authors traced the development of lesions from their earliest stages to the cystic and sclerotic brains, of which one is the subject of the present report. Schwartz has described the earliest lesions in the brain as either areas of haemorrhage, or softening, or of loosening (*Auflockerung*), and followed the subsequent formation of cysts and scars from these initial lesions. He came to the conclusion that most cerebral lesions of infancy, as well as such functional disturbances as asphyxia neonatorum, convulsions, infantile 'tetany', some cases of neonatal jaundice, and many extrapyramidal syndromes could be laid at the door of birth injury. He also suggested that much of the damage may be caused by congestion and haemorrhage from the radicles of the great vein of Galen, resulting from the differential pressure effect (*Minderdruckwirkung*) in the presenting head of the foetus produced by uterine contractions. The relation of prematurity to the incidence of cerebral damage at birth has been the subject of extensive investigations by Ylppö (1919) and by Wail (1950). The latter has been able to show that the argyrophil framework of cerebral blood vessels is incomplete and defective in immature infants, and that extravasations of blood may occur from them even without actual rupture. More recently, Rydberg has challenged some points of detail in Schwartz's observations, and stressed in his turn the importance of the functional disturbances in the nervous control of circulation and respiration at birth and the rôle of such disturbances in the production of cerebral lesions.

In a review of 130 necropsies of mental defectives Benda (1945) found that the cerebral damage could be attributed to birth injury in 24 cases. He also estimated that birth injury could be incriminated in 30% of idiots and in 8% of imbeciles. The contributions of Norman are also of considerable interest and importance. He has not only reviewed and summarized the latest work on the subject (Norman, 1950), but had himself previously reported cases of atrophic sclerosis of the cortex (Norman, 1944) and of *état marbré* of the corpus striatum (Norman, 1947) together with substantial clinical and pathological evidence favouring the natal origin of the brain damage in such cases.

It is extremely difficult to obtain a reliable history of preceding birth trauma in clinically diagnosed

cases of encephalopathy. It is, furthermore, uncertain that a clinically difficult labour is necessarily associated with more severe brain injury. In a series of lumbar punctures performed in normal newborn infants Sharpe and Maclaire (1925) found frank blood in the cerebrospinal fluid in 7% to 13% of all their series of cases. Since haemorrhage is not the only possible brain lesion, and since haemorrhage in areas which do not adjoin the ventricular system or the subarachnoid space would not lead to the appearance of blood in the cerebrospinal fluid, the inference of these observations must be that cerebral damage in the newborn is very frequent. On the other hand Faber (1947) analysed 99 cases of children with established cerebral damage, and concluded from their histories that only 40% were due to natal causes. In an analysis of 618 neonatal deaths Agnes R. Macgregor (1946) has estimated that only 10·5% were due to developmental abnormalities, while intracranial haemorrhage accounted for 27·6% and asphyxia for 13·1% of cases. Experimental work is of limited value since the relative size of the human head at birth is so much larger than that of animals. The approach to this problem must of necessity remain analytical and depend, like that of Schwartz, Siegmund, and other workers on the deductive study of the brains of stillborn children and of children dying in early infancy.

The literature on the subject of brain injuries is very voluminous, but since much of it is both repetitive and speculative, it is possible to refer to the useful summaries provided by Ehrenfest (1922), Ford (1945), Bridge (1949), and Norman (1950). A valuable study of 400 cases of cerebral palsy was recently undertaken by Asher and Schonell (1950) in the Birmingham area. It may be said, however, that considerable confusion and unnecessary disagreement have been caused by the arbitrary definition of the term birth injury. Many workers, who have argued against the importance of birth injury, have interpreted the term in a purely mechanical sense as stretching or tearing. There is no real justification for such an attitude. The violent and complex process of birth involves many far-reaching functional and structural changes, of which the mechanical effects are only one component part.

It is also difficult to justify the attempts of many workers to incriminate one single reaction state like oedema, haemorrhage, tearing, or thrombosis as the sole or chief operative mechanism. These attempts can, perhaps, be partly explained by the implied belief held so commonly by biologists that the quality of interaction between the environment and the individual, of which such states are an expression, remains constant. If that were so it would indeed be reasonable to transpose an effect known to result at a certain stage of the individual's history to another, without gross error. The individual's ontogenesis is, however, not uniform. Stages of relatively gradual and stable development are punctuated by nodal points such as spermogenesis and ovulation, fertilization and birth, at which the quality of interaction between the individual and the environment is different. The significance of any single reaction state at any of these points must be assessed against a particularly rapid and violent complex of other changes. And since the biology of nodal points is at present so imperfectly understood it is unwise to interpret any of its isolated events in any stereotyped and preconceived way. What is pathological at one stage of ontogenesis may well be normal at nodal points and vice versa.

There is much meaning in the following remarks taken from Little's paper.

> 'There is, however, an epoch of existence, viz. the period of birth, during which, at first sight, we might consider that the foetal organism is subjected to conditions so different to those of its earlier and its prospective later existence, that any untoward influences applied at this important juncture affect the economy in a manner different to the influences at work during the periods ordinarily characterized as those before birth and after birth.'

It may be added that later observations and reflection did much to confirm Little's 'first sight.'

Events at nodal points must further be assessed against the background of the individual's past and future history. Birth trauma will tend to damage the larger head of the child of a diabetic mother more than that of an ordinary child. On the other hand, injury to the pyramidal tract at birth will only become apparent at a later age, when the pyramidal tracts begin to function fully. More hypothetically, it is possible to envisage a cortical lesion produced at birth, which only becomes epiloptogenic at an age when that part of the cortex, or areas surrounding it, would normally assume some of their full functional activity.

It must now be considered whether Schob's progressive sclerosing hemiatrophy can be reasonably separated from the remainder of the group of scarred and cystic brains. This can possibly be done to some advantage in the light of the examination of further cases of hemiatrophy, of which another example is reported below.

Case Report

The patient was a boy, admitted to the Fountain Hospital, London, at the age of 2 years and 7 months, who died two weeks later from bronchopneumonia. He was

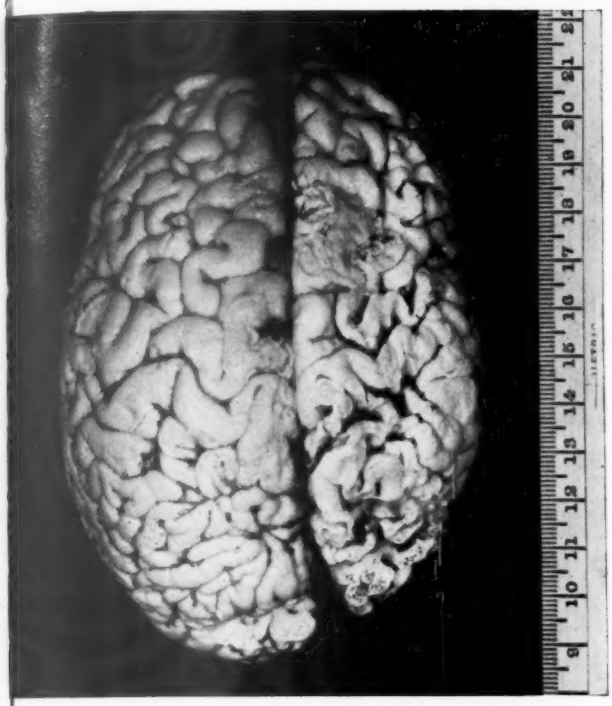

FIG. 1.—Dorsal view of the brain: right-sided hemiatrophy.

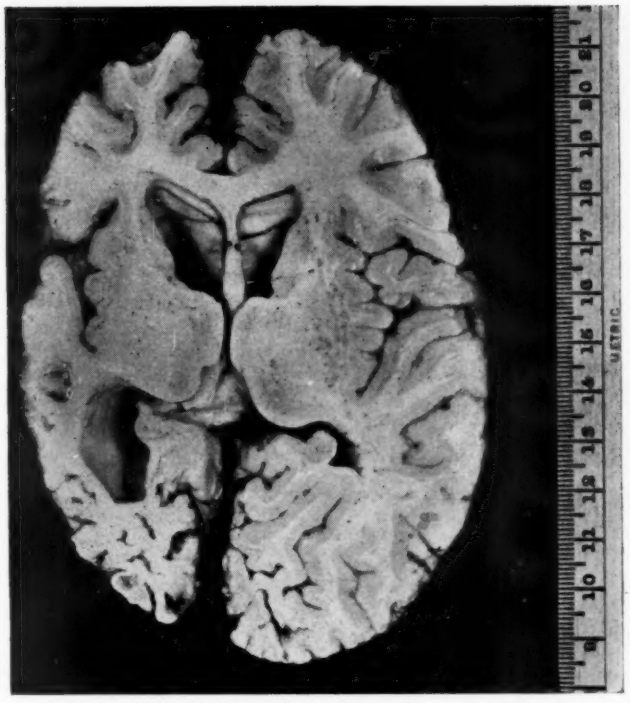

FIG. 2.—Horizontal section of the brain.

the second of three children of healthy working-class parents with no history of mental or nervous trouble in the family, except for a 'nervous breakdown' in a maternal aunt. His older and younger brothers were both healthy. The patient was born after a normal pregnancy, but was five weeks premature. Delivery was said to be normal. His abnormality was first discovered when he had gastro-enteritis at the age of 5 weeks. He then had fits and was found to be blind. He never learned to walk or to talk.

On examination, his pupils reacted sluggishly to light and his left arm and right leg were spastic. He was incontinent and his hearing ability was doubtful. His attitude was restless and he was constantly making purposeless movements and noises. Convulsions were observed during his brief stay in hospital.

Post-mortem Findings. The only relevant findings, besides those in the central nervous system, were seen in the lungs which showed marked hypostatic oedema and a profuse watery mucoid exudate in the trachea and in the main and terminal bronchi.

CENTRAL NERVOUS SYSTEM. The brain was small, weighing 680 g. The dura was adherent to the vertex on the right side. The right hemisphere was 1 cm. shorter than the left. The consistency of the brain was firm, cartilage-like over its posterior part. The gyri over most of the right hemisphere were narrow and the sulci were widened. This appearance was also present in the left hemisphere, but the change there was confined to the occipital lobe. There was a marked depression in the parieto-occipital region over the vertex on the right side and the gyri in that depression showed granular atrophy. The pattern of the gyri was normal throughout the brain, but, in addition to the ulegyria, many of them in the posterior half contained numerous small cortical cysts. The largest of these cysts measured about 0·5 cm. in diameter and the smallest were barely visible (Fig. 1).

A horizontal section through the whole brain showed that the firm white matter was ivory white. This white scarring was also seen in the putamen and in the thalamus on the right side. There was a moderate degree of internal hydrocephalus, similarly more marked on the right side (Fig. 2). All the structures of the brain stem appeared normal to the naked eye. The blood vessels and cranial nerves were normal.

MICROSCOPY. Both hemispheres were divided into horizontal blocks and embedded in celloidin. Sections were also cut from representative blocks taken from the mid-brain, pons, medulla, and the cerebellum. The sections were stained with Heidenhain's haematoxylin for myelin; with thionin, Van Gieson, and Holzer's stain for fibrous glia. Frozen sections were stained for fat with Scarlet R and with Holzer's stain for fibrous glia.

The myelin sections confirmed the presence of ulegyria in the posterior parts of both hemispheres, which was more marked on the right side (Figs. 3 and 4). The forceps major and the digital white matter were greatly reduced in size. Status spongiosus and granular atrophy were present in several parts of the brain, especially in the cortex of the insula, and a marbled state of the myelin (*plaques fibro-myéliniques*) could be seen in some of the gyri covering the insula (Fig. 5). Both pyramidal tracts in the brain stem showed defective myelination and this was more marked on the right side.

Marked diffuse and focal cortical atrophy were the chief histological features. This was most marked on the right side, where, in the more severely affected places, it could be seen to involve indiscriminately all layers of the cortex. The areas of cell loss were in most cases replaced by glial scars (Fig. 6). Some of these areas had,

FIG. 3.

FIG. 4.

FIG. 3.—Posterior half of right hemisphere. Ulegyria.

FIG. 4.—Posterior half of left hemisphere.

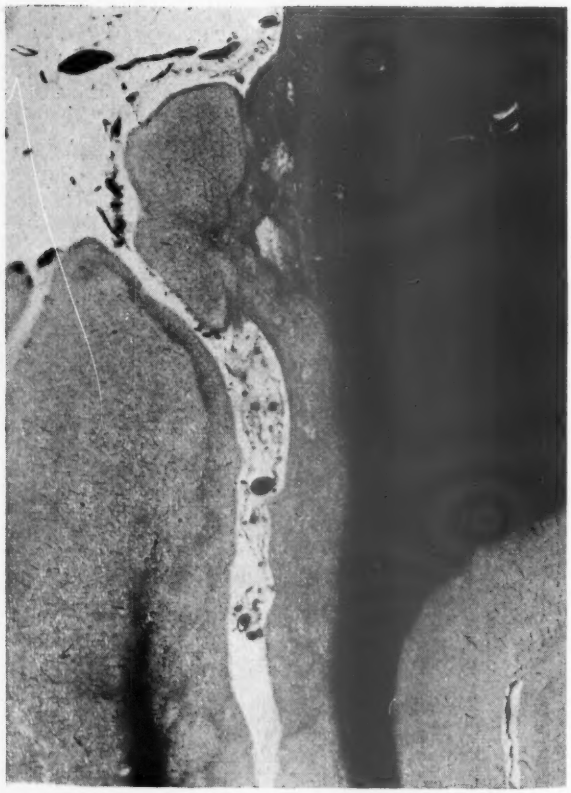

FIG. 5.—Status spongiosus, granular atrophy, and *plaques fibro-myélinques*. Heidenhain's myelin stain × 14·5.

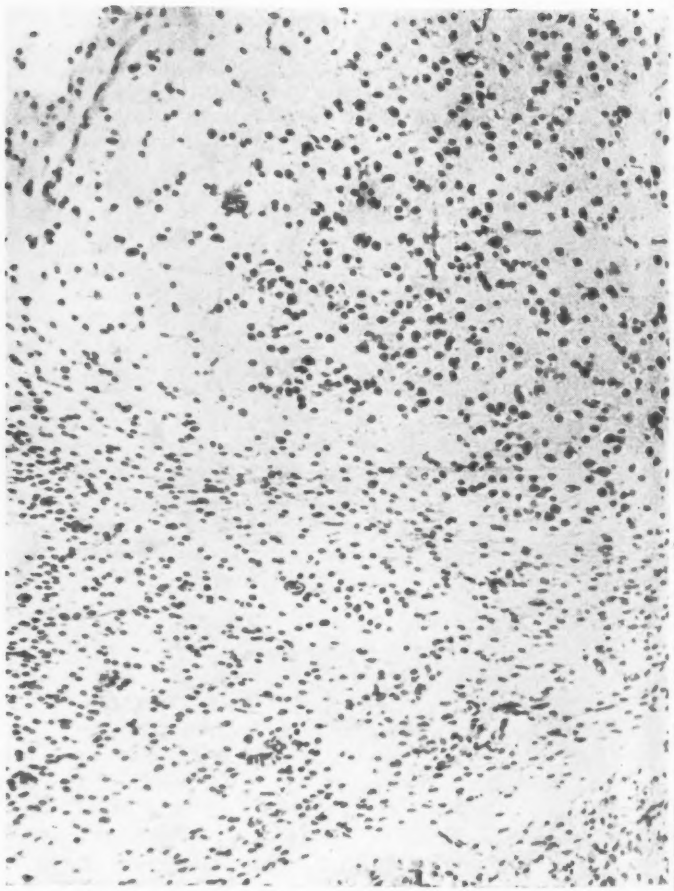

FIG. 6.—Junction of cortex and glial scar. Thionin × 180.

FIG. 7.—Gliosis affecting chiefly the corpus striatum. Holzer stain.

FIG. 8.—Fat in cystic and perivascular spaces. Scarlet R and haematoxylin × 280.

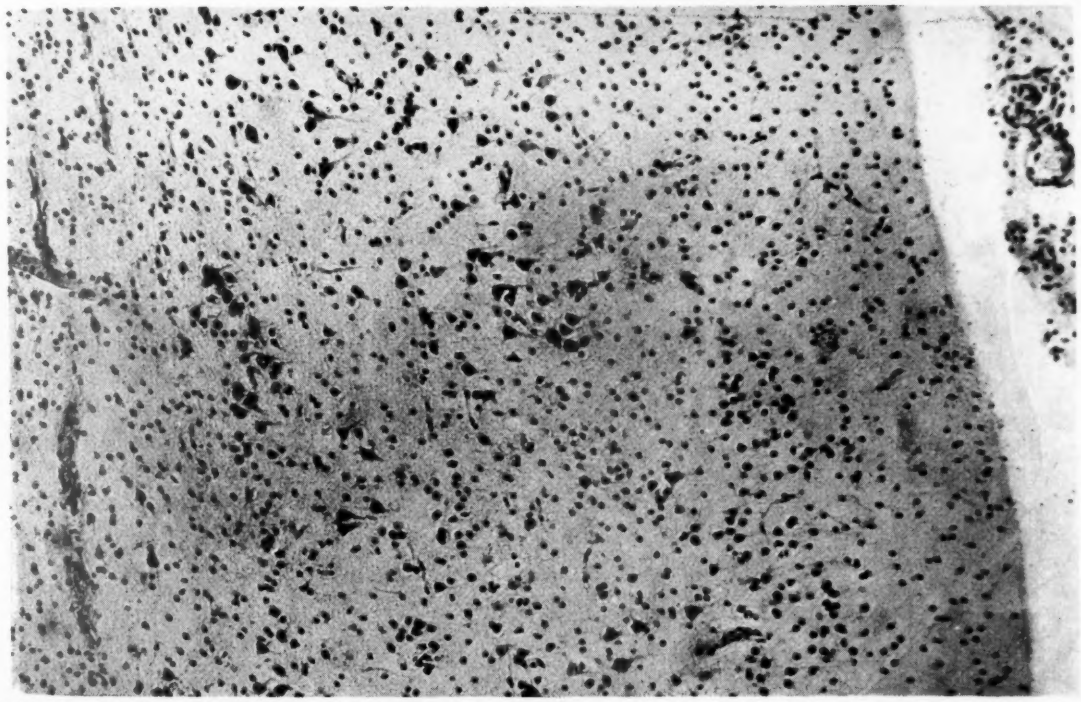

FIG. 9.—Cortex on left side. Loss of nerve cells. Numerous ' ghost ' cells are present. Thionin × 180.

however, remained unrepaired, and a few compound granular corpuscles and blood pigment-containing phagocytes could be seen lying in or near their centre. The transition between areas of cell loss and the more normal cortex was always gradual. Many of the nerve cells in the transitional zones showed varying degrees of degenerative change. In the more normal parts of the cortex, and particularly on the left side, the loss of nerve cells was much more uniform and tended to be systematized affecting one of the laminae, especially the third (Fig. 9). The basal ganglia were also affected. Almost all the cells of the putamen and those in a large part of the caudate nucleus on the right side had disappeared and were replaced by fibrous glia. In addition there were smaller focal lesions in the thalamus. Section from the cerebellum showed some loss of nerve cells and an increase of glia in the dentate nuclei.

Examination of sections stained for fibrous glia showed dense gliosis of both cortex and the white matter of the cerebrum. This gliosis was not uniform. In places it was confined to the white matter stopping short of the cortex. In other places it affected the cortex also. Numerous microcysts and larger cystic cavities were seen in the gliosed areas. The gliosis of the basal ganglia on the right side corresponded to the areas of cell loss described above (Fig. 7). There was also marginal, peri-aqueductal, and periventricular gliosis in the brain stem and in the area of the dentate nuclei of the cerebellum.

Sections stained for fat showed numerous fat-laden phagocytes in the cortex on the more affected side. These were distributed both diffusely and in dense foci round blood vessels and in the smaller cysts (Fig. 8). In the less affected areas, particularly on the left side, fat cells were distributed less densely and more uniformly throughout the cortex.

In addition there was some fibrosis of the leptomeninges and thickening of some of the cortical blood vessels. No thrombi were found in them.

Discussion

The character and distribution of the lesions in this case indicate the end-result of destructive processes. The general picture closely resembles that shown by Schwartz and by Siegmund to follow birth injuries. The history of prematurity and the known association of such prematurity with an increased incidence of brain damage further support this conclusion. The predominantly posterior localization of the lesions and their topographical systematization in the basal ganglia is in agreement with the suggestion made by several workers in the past regarding the vulnerability of the radicles of the vein of Galen to birth injuries.

While the focal character of many lesions and the abundance of fat-laden cells place this case in the group of lobar ulegyria, there are also many lesions in it, particularly in the less affected areas of the brain, which correspond to those described in the progressive sclerosing variety of hemiatrophy. It seems possible that the more insidious and uniform changes found in the latter condition could be the result of less severe initial lesions and a more protracted course. Further case material is therefore desirable in order to establish the validity of its nosological entity.

Summary

The literature relating to hemiatrophy of the brain is reviewed and its possible aetiology discussed. A case of hemiatrophy is reported and it is suggested that it followed birth injury associated with prematurity. The nosological position of progressive sclerosing hemiatrophy of Schob is also discussed.

I wish to thank Professor A. Meyer for his advice and helpful criticism.

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THE INCIDENCE OF PYLORIC STENOSIS IN DUNDEE

BY

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(Received for Publication April 3, 1951)

The mechanisms whereby pyloric stenosis develops are unknown. As a genetic factor is probably concerned in the aetiology, and as race differences in the frequency of the disease have been observed, it seems desirable that the incidence in a community should be recorded whenever the opportunity arises.

The city of Dundee is well situated for a study of the incidence of a disease which necessitates admission to hospital, as geographical considerations make it almost certain that any case arising within the city will be admitted to one of two hospitals.

This report refers to all cases of pyloric stenosis admitted during the seven years 1940 to 1946. During this period there were 84 cases, of which 32 were in families living within the city boundaries: only these 32 are included in this series, thus enabling the incidence to be expressed as a proportion of the total live births in the city during the same period.

These figures necessarily refer to what Davison (1946) has called the 'manifest incidence' of the disease. There may well have been a few mild cases of the kind which Wallgren (1941) and others describe, in which recovery took place spontaneously but in which radiological examination would have enabled a diagnosis to be made. Every case recorded here was severe enough to leave no clinical doubt about the diagnosis, which was in each case confirmed at operation.

It is fortunate that during this period no physician on the staff of either hospital was treating cases without operation. It is also known that no surgeon on the staff of either hospital treated any case in a private nursing home during this time, and that no post-mortem examination was performed in the city on a case undiagnosed during life.

Of 21,288 live babies born during these seven years, 32 developed pyloric stenosis, of whom 23 were boys and nine girls, giving an overall rate of 1·5 per 1,000 live births, or a rate in male births of 2·1 per 1,000 and in female births of 0·9 per 1,000. These results are tabulated and are compared with the figures published by Davison for Newcastle and by Wallgren for Gothenburg. The rate observed in Dundee differs significantly from that observed in Gothenburg; this difference is great enough to suggest a real genetic difference between the two populations. The differences between Dundee and

TABLE 1

RATES OF INCIDENCE OF PYLORIC STENOSIS IN THREE CITIES

	Live Births	Cases	Incidence per 1,000 Live Births	S.E. of Sample
Dundee, 1940–46 ..	21,288	32	1·5	0·26
Newcastle, 1939–42 ..	17,457	49	2·8	0·40
Gothenburg, 1934–40 ..	25,642	102	4·0	0·39

TABLE 2

SIGNIFICANCE OF DIFFERENCES BETWEEN OBSERVED RATES

	Difference/ 1,000 Live Births	S.E. of Difference	Significance	
			P=0·05	P=0·01
Dundee/ Newcastle ..	1·3	0·5	+	−
Dundee/ Gothenburg	2·5	0·5	+	+
Newcastle/ Gothenburg	1·2	0·6	±	−

Newcastle and between Newcastle and Gothenburg are barely significant.

Conclusions

The observed incidence of pyloric stenosis, 1·5 cases of congenital hypertrophic pyloric stenosis per 1,000 live births, in a seven year study of Dundee probably indicates a true incidence of between 1 and 2 per 1,000 live births.

My thanks are due to the physicians and surgeons of Dundee Royal Infirmary and of Maryfield Hospital for their cooperation and for permission to publish my findings, and in particular to Dr. James Thomson in whose department the work was carried out.

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FURTHER TECHNICAL PROBLEMS IN METABOLIC INVESTIGATIONS IN CHILDHOOD

BY

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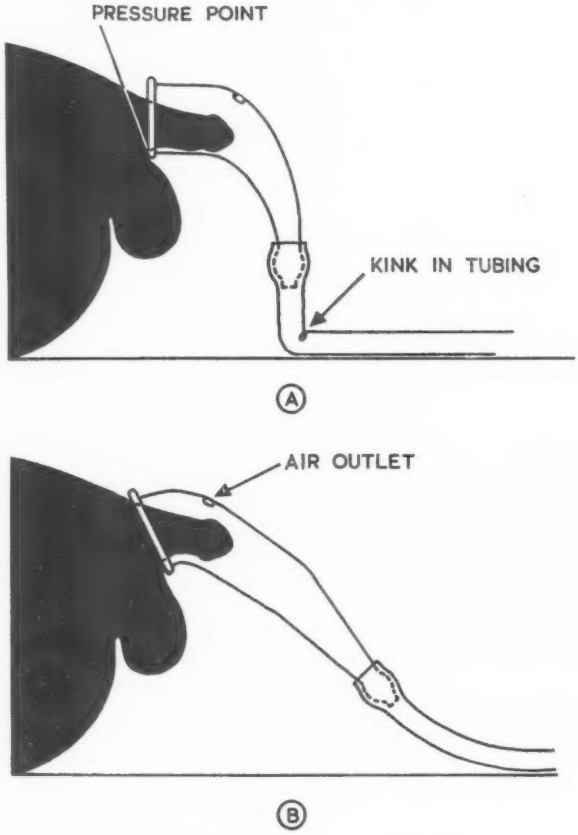
(Received for Publication March 14, 1951)

The purpose of this article is to describe two types of apparatus which have been found useful in the collection of urine from male and female infants, and also some modifications of the methods previously published from this unit (Edmunds, 1950). The method used for the male infants is based upon that described by Edmunds, but that used for the female infants employs a technique which does not appear to have been described previously.

The collection of urine from female infants has always presented considerable technical problems, and only two papers appear in the English and American literature on this subject. Cohen and Blatt (1940) in America described an apparatus for use with female infants employing a rubber unit with a recess tapered to form a funnel-like spout to which was attached glass tubing to be connected with a length of ordinary rubber tubing. In order to prevent faeces from being forced upwards into the collecting apparatus a small rubber button was made in the lower part of the apparatus to fit between the anal opening and the lower part of the vagina. We have not used this apparatus, though the method to be described also makes use of perineal pressure to divide the faeces from the urine. Four years later Thomson (1944) published a description of an apparatus for use with newborn infants. We have followed his description, but were unable to achieve satisfactory results in older infants. The method employs an ordinary rubber rat-tail aural syringe, in which is cut an oval hole to fit over the labia majora. We were unable to prevent contamination of the urine by faeces, and also felt that there was some risk of trauma from the hard rubber, as, in order to achieve a water-tight junction with the skin, considerable pressure had to be applied.

Apparatus for Collecting Urine from Male Infants

The method previously described by Edmunds has two disadvantages. Designed for use with premature infants, it is only suitable for relatively immobile subjects, and requires the use of stockinette combinations with an elastic loop by which the glass collecting tube is fixed. For older children this is insufficiently rigid, and the



A. SHOWING DISADVANTAGES OF THE ORIGINAL SHAPE OF GLASS TUBE.

B. SHOWING THE MODIFICATION OF THE ORIGINAL SHAPE.

FIG. 1.

shape of the glass tube is such that it cannot be used with the infant lying on its back, as may be necessary if an intravenous infusion is set up. Also the use of the combinations makes it difficult to splint the legs for intravenous therapy, and if an intravenous infusion is already running the combinations cannot be put on.

It was decided therefore that some form of apparatus might be designed for use with an ordinary mattress and cot; that is, for occasions when the collection of urine alone is required. The second requirement was that the apparatus should be capable of being set up without unduly disturbing an ill child on intravenous therapy.

To illustrate the principles involved in the design of the glass collecting unit for male infants Fig. 1 shows the difficulties in using a tube of the original shape with a child lying on its back on an ordinary mattress (one without any holes for the passage of tubes, etc.). The first difficulty is that with a tube with a right-angle bend all the pressure comes on the base of the penis at the junction with the scrotum. The second difficulty is that the rubber tubing has to be bent at a right-angle and is liable to kink or to push the glass tube upwards. A glass tube was therefore designed which exerted an equal pressure all round the base of the penis and whose long axis was more nearly parallel with the mattress.

The second problem of fixing the tube in position was solved by using an ordinary rubber hernia truss (Fig. 2). This is strapped round the lower abdomen in the usual way, but the two round rubber strips passing between the thighs are left as loose-fitting as possible. These rubber strips pass on either side of the glass tube and can be made to grip it tightly in position by tying them together below, and, if necessary, above the glass tube (Fig. 3). This method of fixation does not produce any undue pressure or discomfort and can be kept in place for a number of days. For this method, as for others, using an ordinary mattress, it is of course necessary to tip the bed with blocks, and therefore the infant may need to be anchored by pillows by pinning an abdominal binder to the bottom sheet, or by tying a restraining jacket to the sides of the cot.

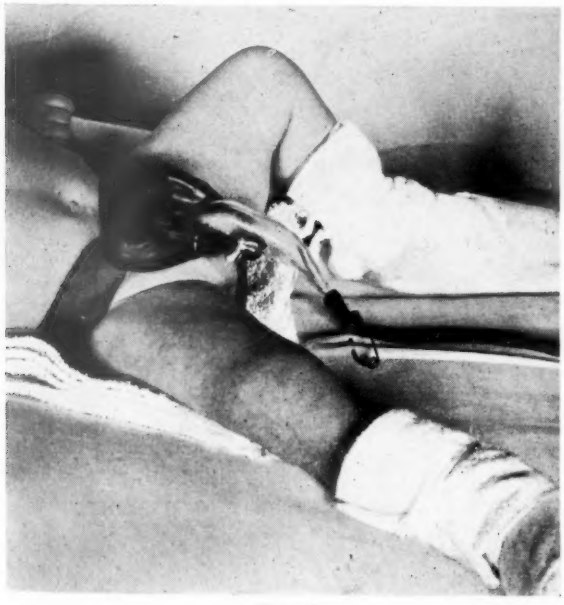


FIG. 2.

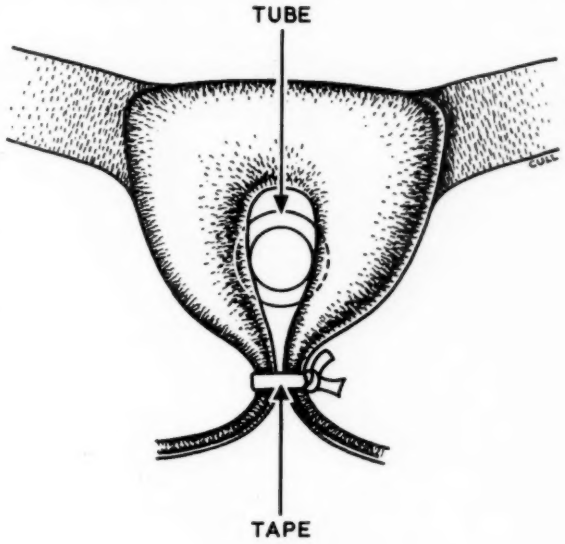


FIG. 3.

Apparatus for Collecting Urine from Female Infants

The technique described has proved successful with a number of female infants varying in age from 3 months to 4 years, the oldest child being a severe ament with phenylketonuria. Some difficulty was experienced with a very oedematous girl with type II nephritis, and the use of the apparatus had to be stopped on account of the development of a superficial blister and oedema. Apart from this no ill-effects have been noted.

The first problem was to obtain an accurately fitting apparatus, as it was found that unless this was achieved there was always some leakage in the perineal region. The second problem was to find a substance which could be moulded accurately and conveniently. On the advice of the dental department of the hospital the plastic known as 'welvic'* P.V.C. paste (Baird, 1948) was used.

The technique adopted was as follows. A female infant of the required size was selected and a 'zelex'† impression was made of the whole of the perineal region, to include the labia majora and the anal orifice. From this impression a plaster model of the perineum was made and a wax prototype was built on this to fit exactly (Figs. 4 and 5). A mould was then made from the wax prototype and the liquid plastic was then poured into the mould and heated in an oven at 130° C. for 30 minutes.

* 'Welvic', polyvinyl chloride paste, is obtained from Imperial Chemical Industries Ltd. (Plastics Division).

† 'Zelex', alginate impression material, is obtained from the Amalgamated Dental Co., Ltd.

The shape of the apparatus is shown in the photographs and in Fig. 6, the main points being (1) an accurate fit at the region of the perineal body, (2) sufficient size to enclose the labia majora, (3) adequate capacity to take

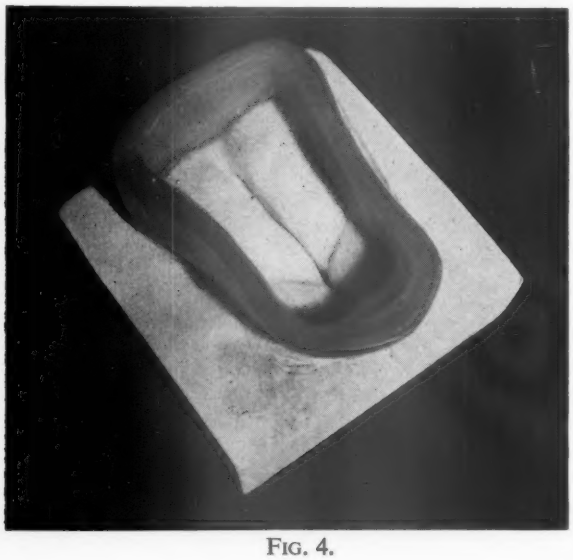


FIG. 4.

up a rapid flow of urine without overflowing, (4) drainage from the most dependent portion of the apparatus, and (5) an air-outlet at the top of the apparatus.

It was at first thought that a new apparatus would have to be made for each child, but this has proved unnecessary as one size will fit children varying quite considerably in size and age. We have used three sizes only and have not yet had to make any intermediate ones. The plastic is quite soft, and even when applied

FIG. 5.

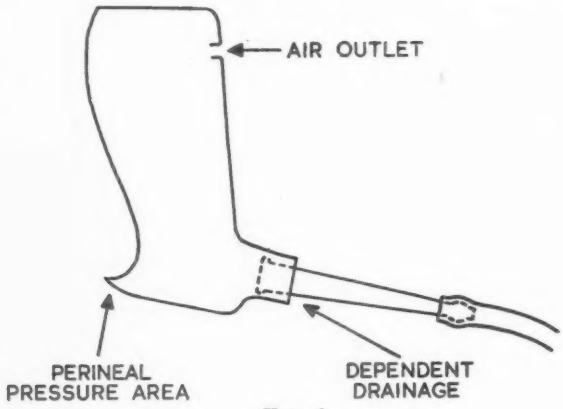
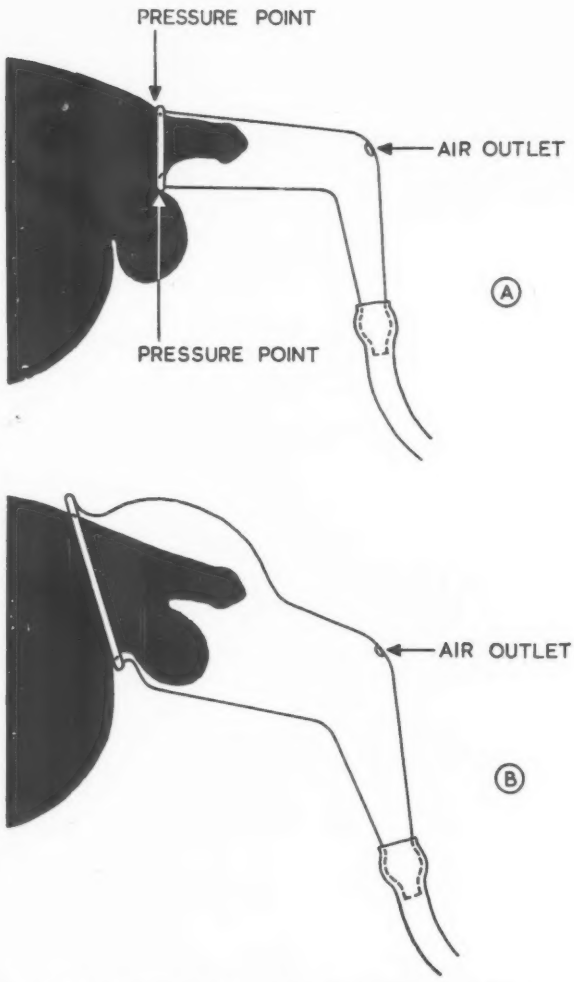


FIG. 6.



A. SHOWING ORIGINAL DESIGN, WITH POINTS WHERE PRESSURE IS LIKELY TO OCCUR.

B. SHOWING THE MODIFICATION OF THE ORIGINAL DESIGN.

FIG. 7.

for periods up to four days has produced no trauma except in the oedematous child. The apparatus is held in place by a small binder with a hole through which passes the outlet tube (Edmunds, 1950). If used in an ordinary cot this has to be tipped, and the child's buttocks may have to be placed on pillows in order to provide sufficient clearance for the glass outlet tube. The only disadvantages of the P.V.C. paste are that it cannot be boiled, and is dissolved by acetone, chloroform, and similar substances. After use the apparatus is scrubbed with soap and hot water and can be sterilized by immersion in antiseptics of the 'dettol' type.

Recent Modifications in General Technique

Recently we have used a pre-vulcanized natural rubber latex ('vuljex'*) which has two advantages; first it sets without heating, and secondly it can be sterilized by boiling.

During the past year a number of modifications have been made in the techniques originally published from this hospital (Edmunds, 1950). Though they do not represent major alterations, it is felt that even small changes may make a great difference in the comfort of the child and in the success of the balance experiments.

Markers. It has been found more satisfactory to give carmine as a dry powder in a dose of 4 grains, as this is relatively tasteless compared to the solution originally recommended.

Collecting Urinal. This is designed for the metabolic bed. The original pattern fitting over the penis caused some discomfort by pressure and has been replaced by one fitting over the scrotum and penis. To prevent any pressure in the dorsum of the penis a bulge has been made on the upper surface of the urinal (Fig. 7).

Canvases and Binders. A number of sets of canvases and binders have been made to fit children of different sizes. Pressure sores can be prevented by placing pads of gamgee tissue round the buttocks, thighs, and under the axillae, and rolls of napkins are placed under the thighs to prevent undue dragging on the binders round the thighs. Large blanket pins are stronger than any safety pins and cannot easily be swallowed.

Position of the Child. Many children can sit up on the bed with pillows behind the back if the top binder is removed during the day. This makes feeding and bringing up wind very much easier, and enables the children to take an interest in their surroundings.

* 'Vuljex', pre-vulcanized centrifuged natural rubber latex (type 5), is obtained from Wm. Symington & Son, Ltd., 36 Gracechurch Street, London, E.C.3.

Summary

The technique and apparatus used in the collection of urine from male and female infants are described, and also some recent modifications in general technique.

Acknowledgments and thanks are due to Professor Moncrieff and to Dr. W. W. Payne for their help and advice, to Sister Merrilees and her staff, to Mr. D. P. Walther, Orthodontic Registrar, to the technicians of the dental department, The Hospital for Sick Children, and to Mr. Derek Martin and to Mr. P. Cull (The Hospital for Sick Children) for the photographs and diagrams.

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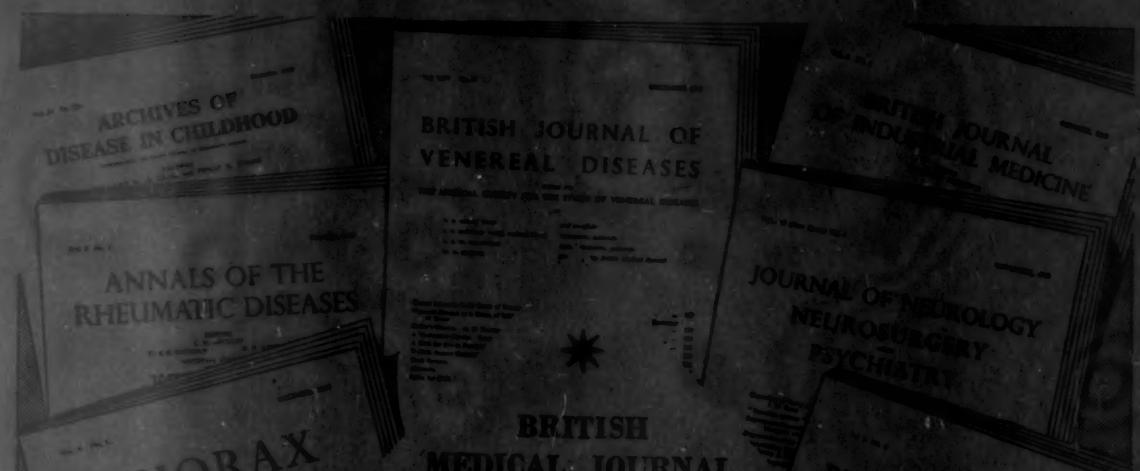
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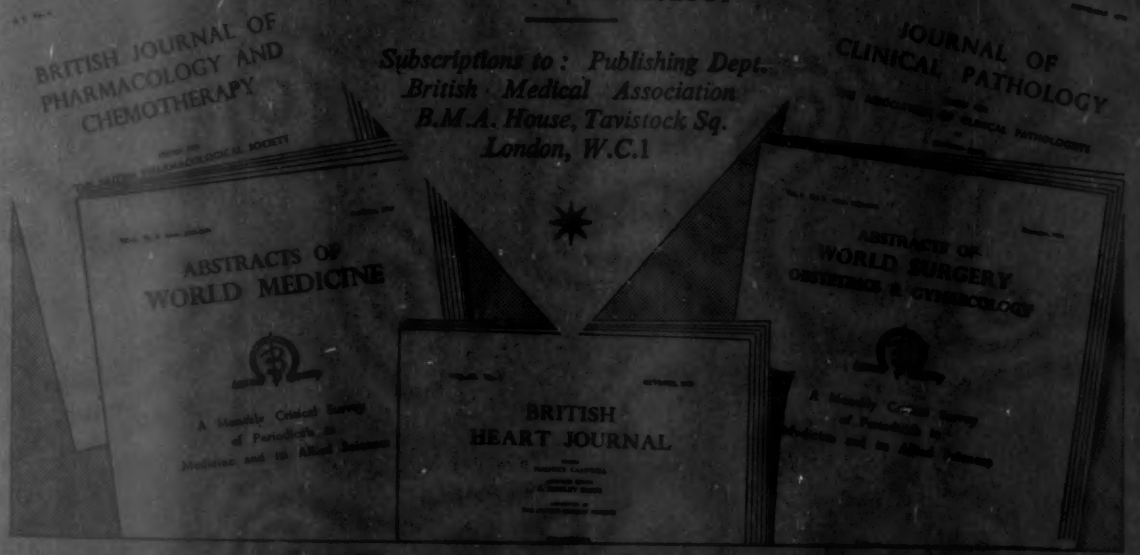
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Specials diets are ordered in the treatment of many illnesses, and in some cases foods that normally supply the B vitamins are restricted. Supplements of these vitamins may therefore be required.

Many authorities consider it an advantage to give a natural source of the vitamin B_2 complex, in which the individual factors are present in balanced amounts. Marmite is a yeast extract which provides naturally occurring B_2 vitamins, and it is therefore frequently prescribed as a dietary supplement.

MARMITE

yeast extract

contains

RIBOFLAVIN (*vitamin* B_2) 1.5 mg. per oz. NIACIN (*nicotinic acid*) 16.5 mg. per oz.
Obtainable from Chemists and Grocers
Special terms for packs for hospitals, welfare centres and schools

5180 THE MARMITE FOOD EXTRACT CO., LTD. 35 SEETHING LANE, LONDON, E.C.3

Literature on application

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